BRAIN

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A Journal of Neurology

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MARCH, 1954

BRAIN

VOL. 77, PART 1.

MECHANISMS OF VOLUNTARY MOVEMENT[1]

BY

WILDER PENFIELD

(*From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute*)

NEUROLOGISTS, physiologists and anatomists alike have been content, in the past, to trace sensory pathways upward to the cerebral cortex and other pathways downward toward the spinal cord and muscles. Many have looked upon the cortex as a sort of Mount Olympus of the mind where reason seemed to dwell and where the soul made its mysterious contact with the body. There at the top of the mountain each functional area of the brain was thought to be somehow connected and co-ordinated with the others by means of transcortical association tracts.

There is enough evidence available from the study of the human brain for consideration of the problem of voluntary movement on a physiological basis. Neurologists should examine the evidence objectively, without the bias from current clinical teaching.

PREAMBLE

During voluntary movement, as distinguished from reflex movement, it is clear that the cerebral cortex plays an important role. I propose to place before you a consideration of the nature of this role in the light of evidence from the study of man. Some of the evidence[2] is derived from observations during neurosurgical operations.

[1]The Medical Research Society Lecture, London School of Hygiene, London. July 6, 1953.

Presented in part as the Falvelle Medallist's Address—Royal Society of Canada, Montreal, June 4, 1951.

[2]In the course of well over 700 craniotomies under local anæsthesia, it has been my lot to study and make records of the activity of the cerebral cortex of men who were fully conscious. In the great majority of these cases cortical excision was carried out as treatment for the focal epileptic seizures from which these patients were suffering. In justification of the surgery it may be said that this procedure has eventually proved itself a so-called cure in about 50 per cent of the cases.

It should not be necessary to point out that surgical procedures are never primarily experimental. Nevertheless, for the clinician who waits hopefully, chance often fulfils the most exacting requirements of physiological observation, and little by little time fills up the gaps in the evidence.

At recurring intervals these records have been re-studied from different points of view. These studies and the accumulating observations of others form the material for the present essay.

The preamble of a study, like that of a play, may foreshadow the argument that is to follow. So it may be said that the human cerebral cortex cannot satisfy the Olympian demands of those who would consider it a highest level of association and integration. It does not contain the neurone mechanism for final integration of the nervous activity of the brain although it contributes essential services to that integration. On the contrary, each functional area of the cortex seems to play its role in conjunction with the activity of related subcortical units of integration.

Somatic Motor and Sensory Areas of the Cortex

Three areas of cerebral cortex are devoted to somatic movement and sensation as outlined in fig. 1.

(1) *Rolandic motor* (*precentral*).—The primary motor area which gives

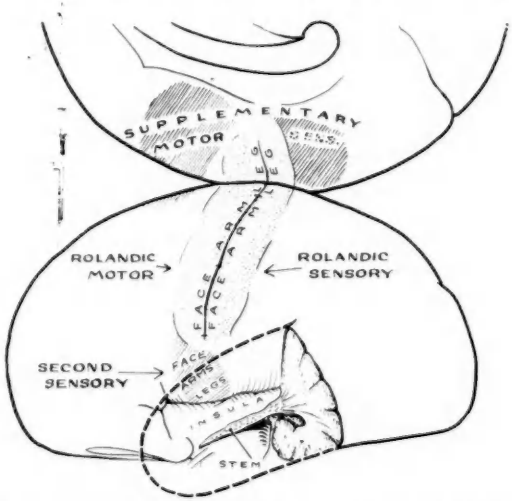

Fig. 1.—Somatic motor and sensory areas of the cerebral cortex of man as outlined by electrical stimulation. Rolandic motor and sensory—Precentral gyrus predominantly voluntary motor, postcentral gyrus predominantly sensory. Supplementary motor—Predominantly concerned with voluntary movement, but also sensory. Second sensory—Predominantly sensory but occasionally exerting (inhibitory) control over voluntary movement.

rise to the cortico-spinal tract was first demonstrated by electrical stimulation in the experiments of Fritsch and Hitzig (1870; also Hitzig, 1874) and subsequently established by anatomical study.

(2) *Supplementary motor.*—Munk (1881) followed by Horsley and Schäfer (1888) showed that, in monkeys, movements of the contralateral arm, also head turning, could be produced by stimulation of cortex within the longitudinal fissure situated anterior to the primary leg representation. Grünbaum and Sherrington (1901–1902, 1903) and Sherrington and Grünbaum (1901), studying anthropoid apes, pointed out that movements of foot and leg, shoulder and chest, thumb and fingers, could be produced in the same area. They expressed the opinion that "the conditions of obtainment of these reactions separate them from those characterizing the 'motor' area."

In man, during operations carried out under local anæsthesia, it has been possible to establish the fact that there is, within the longitudinal fissure, an area from which somatic movements, including vocalization, are obtained, an area of cortex functionally separable from what may be called the Rolandic or primary motor strip. We have called this the "supplementary motor area" (Penfield, 1950; Penfield and Welch, 1951) for purposes of description.

(3) *Second sensory.*—More recently physiologists (Adrian, 1940; Woolsey, Marshall and Bard, 1942) demonstrated the existence in laboratory animals of a second sensory area in the cortex by the method of evoked potentials.

Following this experimental demonstration in animals we were able to verify the existence of a second sensory area in man repeatedly from 1946 onward (Penfield and Rasmussen, 1950). It is situated on the cortex below the lower end of the precentral gyrus and extends down into the fissure of Sylvius on its superior bank (fig. 1).

The supplementary motor and the second sensory areas in the human cortex doubtless play a role in normal voluntary motor mechanisms, but it is largely a dispensable function, if one may judge from the results of unilateral excision.

All three of these somatic areas are, to a differing extent, involved in the mechanisms of movement and of sensation as well. The Rolandic cortical strip is concerned with movement (chiefly precentral gyrus) and sensation (chiefly postcentral gyrus) in the opposite parts of the body. Its removal results in paresis. Other bilateral effects will be discussed below.

On stimulation, the supplementary motor area gives many motor and inhibitory responses and few sensory responses. The second sensory area gives many sensory responses and occasional inhibitions of voluntary movement.

Each area probably makes a contribution to the efficiency and dexterity of voluntary motor performance. Removal of either one of the

extra-Rolandic areas produces no clinical deficit except perhaps a slowing down of repetitive or alternating contralateral movements in the case of the supplementary motor area. It is not known what the effect might be of bilateral removal of these areas. One may surmise that, under normal conditions, the supplementary motor area exerts its influence upon the maintenance of postures, and the execution of repetitive manœuvres especially those that include the whole body. Both of these areas are more involved in contralateral movement and sensation than in ipsilateral but neither is exclusively related to one side.

The precentral gyrus may be said to play a primary role in voluntary activity; the extra-Rolandic areas a secondary and more dispensable role.

The Stream of Impulses that Produce Voluntary Movement

It is obvious that the nature of voluntary action is determined according to sensory information, but also according to the guidance of memory and the conclusions of reason. This means that there must be a neural mechanism within the central nervous system capable of producing complicated integration before the appropriate motor impulses are delivered to the precentral gyrus. In the following discussion it must be recognized that certain forms of voluntary action may well be mediated through other "centres" as well as the precentral gyrus.

When one considers the extraordinary dexterity of hand movement it is obvious that, if the precentral motor gyrus is to be utilized in the execution of skilled acts, the nerve impulses that reach it must come in a pattern which is vastly varied, varied in time of arrival, in rhythm and in the combination of ganglion cells selected for activation.

One conclusion in regard to the origin of these patterned impulses may be established at once. They do not come directly across the neighbouring cerebral cortex to the precentral gyrus, for if the gyrus immediately in front of the precentral gyrus is excised, the skilled act may still be carried out, and if the postcentral gyrus immediately behind it is excised, the act is not abolished either, although it may become awkward (*see* fig. 2).

Therefore, the controlling impulses flow upward to the precentral gyrus from some subcortical position. The impulses in this subcortico-cortical stream pass to the precentral gyrus and from there downward again to the bulbo-spinal grey matter on the way to the muscles (*see* fig. 3). These impulses arrive in a sequence, a pattern which produces the motor activity that the man intended to carry out.

It seems reasonable to assume that this volitional stream of impulses must originate in ganglionic nuclei which have functional or preparatory connexions with the sensory and elaborative areas of both hemispheres. It is to be expected that all the functional subdivisions of the cortex of

each hemisphere must be in direct relationship with the system in which these nuclei are placed.

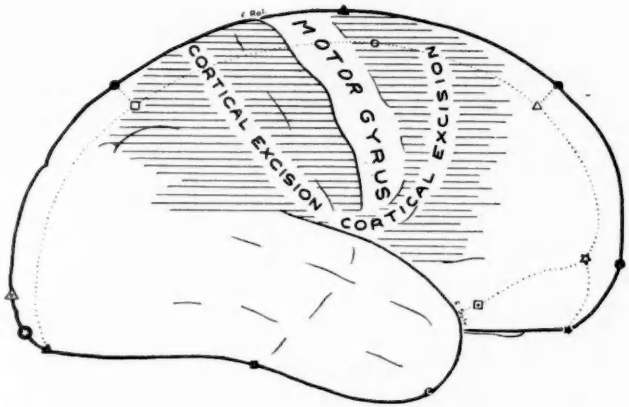

FIG. 2.—Precentral (motor) gyrus can be employed for dexterous voluntary movement even after interruption of transcortical tracts by excision of surrounding gyri.[1]

Because of the bilateral neurone connexions this system may certainly be considered bi-encephalic. It is the central co-ordinating integrating system which we may call centrencephalic. A number of useful purposes can be served by giving this hypothetical system a name, such as centrencephalic (Penfield, 1952*a*). But it must be recognized that this is a functional complex that is not isolated from the cortex or other anatomical areas. It seems likely that the major portion of the mechanism is located in parts of the diencephalon, mid-brain and pons—the higher brain-stem which includes the two thalami (fig. 4).

Only within a centrencephalic system of this sort could a stream of willed impulses be initiated, capable of producing the action that is appropriate to all previously received information. Only thus could the stream of impulses going to one precentral gyrus be co-ordinated with the stream that is going out to the precentral gyrus of the other hemisphere.

ELECTROCORTICOGRAPHY DURING VOLUNTARY ACTION

The suggestion that the stream of impulses that produces voluntary utilization of the precentral gyrus does actually impinge upon that gyrus from below is consistent with the following observations. The normal

[1] In many human cases block excisions of cortex have been made in front of, or behind, the precentral gyrus and this was not infrequently combined with excision of the motor face area. In one case complete excision of all neighbouring cortex was carried out at one operation leaving only the precentral arm and leg areas.

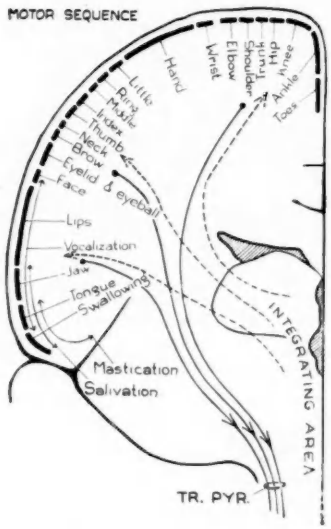

FIG. 3.—Motor sequence in the precentral gyrus. Frontal section has been made through right hemisphere. The stream of nerve impulses, that produce voluntary action, is indicated by arrows from zone of origin somewhere in the integrating area (centrencephalic system) to motor gyrus and onward in the corticospinal tract. The black segments drawn in the cortex indicate the location and comparative extent of representation of movement of each body part. Representation signifies the connexions of gyrus with contralateral anterior horn formation of spinal cord and medulla. The location of cortical control of the subcortical mechanisms of vocalization, salivation and mastication varied so much in position within the sequence from case to case that it was necessary to indicate the position of each by overlapping lines although the representation was not extensive in any individual case. (*From* Penfield and Jasper, 1954.)

rhythm[1] of the cortex adjacent to the central fissure is 18 to 30 beats per second. This is called beta rhythm.

Professor Herbert Jasper and I reported the following observation in 1949, and we have verified the findings repeatedly since that time.

In the case reported the patient was an intelligent adult. The left hemisphere was exposed under local anæsthesia. The central area appeared normal. Eight recording electrodes connected in serial pairs were placed on the cortex and after an exploratory run they were placed on and about the Rolandic sensorimotor strip. A practically "pure beta

[1]It is well known that when a normal individual lies relaxed and with his eyes closed, the electrical potentials of his brain beat in certain standard rhythms. Over the posterior portion of the brain the rate of the brain wave rhythm is 12 per second. This is called the alpha rhythm. It may be called the resting rhythm, for if the individual opens his eyes so that the occipital lobes receive visual impulses from the retina the alpha rhythm is broken up and disappears.

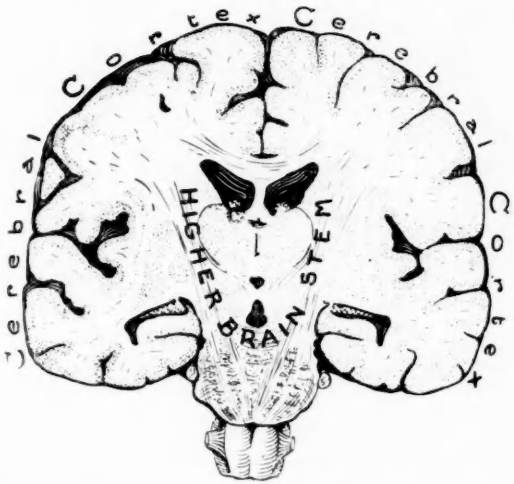

FIG. 4.—Frontal section through the brain of man. The brain-stem, as defined by Herrick (1920), includes "all of the brain except the cerebellum and the cerebral cortex and their dependencies." Thus defined, the brain-stem includes the thalami. The centrencephalic integrating system is that neurone system within the brain-stem (diencephalon, mesencephalon and probably rhombencephalon) which has bilateral (symmetrical) functional connexions with the cerebral hemispheres.

rhythm," with regular waves at about 25 per second and 100 to 250 microvolts in amplitude, was recorded while the patient was relaxed. This was to be considered the resting rhythm of the sensorimotor strip.

When the patient was asked to place the fingers of his right (contralateral) hand one after the other on his thumb, and, when he did so, the beta rhythm vanished from the record of the electrode placed upon the precentral and postcentral hand areas, but it continued unaltered in the motor and sensory face area. It continued unaltered also in the cortex anterior to and posterior to the Rolandic strip (*see* fig. 5).

During this procedure the patient was listening to all that went on in the operating room. When he heard the request to move his hand, and when he moved that hand, a change occurred in the corresponding portion of the central cortex. The resting beta rhythm disappeared due, one may assume, to the arrival of activating impulses in the hand area. This might be considered somewhat analogous to the abolition of the alpha rhythm in the occipital areas when visual impulses reach the visual cortex.

It is a fact of further interest that if the patient clenched his fist, the beta rhythm vanished likewise, but as he continued to clench the fist, it returned. This suggests that the continuance of a predetermined posture is possible without the arrival of a continuing stream of impulses at the precentral gyrus.

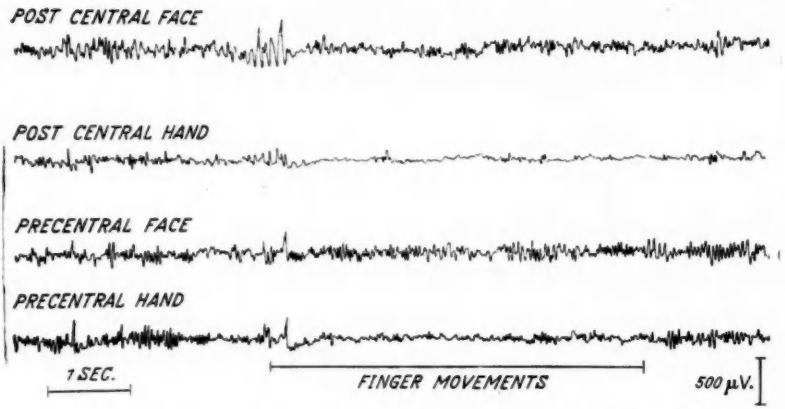

FIG. 5.—Electrocorticogram. Resting beta rhythm disappears in hand area but not elsewhere on command to move fingers (*see* text). (*From* Jasper and Penfield, 1949.)

On the other hand, if he carried out a series of acts such as touching his thumb with one finger after the other, the resting beta rhythm did not return. This alteration in rhythm does not occur in other parts of the cortex when the hand is moved. Moreover, it is not due to the sensory effect of the movement, for when the patient is told to get ready to move his hand on a given signal, the beta rhythm also disappears with that warning. That is to say it disappears before the final signal is given, and before the hand is moved.

It seems reasonable to conclude that the impulses which abolish the resting rhythm of the motor hand area reach the precentral convolution from some subcortical source, and not across the cortex from auditory or visual areas in the same hemisphere. It seems likely that these are the impulses which produce voluntary action although, one must admit, such observations alone do not finally prove it.

ROLANDIC MOTOR FUNCTION AND SUBCORTICAL MOTOR MECHANISMS

Removal of the precentral gyrus of an adult without subcortical injury produces paralysis of the arm and of the leg on the opposite side of the body with no observable sensory defect.

But eventually some recovery occurs. This recovery is more rapid in the leg, so that the man walks in a few months and does quite well except for some spasticity of the limb and inability to wiggle his toes. Arm movement returns more slowly, first in the proximal joints and eventually to a limited extent in the hand and fingers. Capacity for independent finger skills never returns.

But the precentral gyrus is not the only ganglionic collection that is used for voluntary action. When a newborn babe draws his first breath

he begins to move the proximal joints of arms and legs. He vocalizes and soon he sucks and swallows in a very skilful manner. But he cannot use his fingers in any skilful act. If he receives an injury to the cortex there may be little or no evidence of disability until he passes his first year of life. Then, when skilful employment of the hand and foot normally appears, the defect first becomes apparent[1].

It seems possible then that when the baby first moves he may not employ his cortex at all. He moves the proximal joints quite well, he swallows and he vocalizes.

The adult who has lost his motor convolution can do the same. The difference is that he directs his movements with greater intelligence. He swallows and vocalizes and, after a period of initial paralysis as has been said above, he moves upper and lower extremities quite well at the proximal joints, and he walks.

An organization like that shown in fig. 6 might conceivably provide

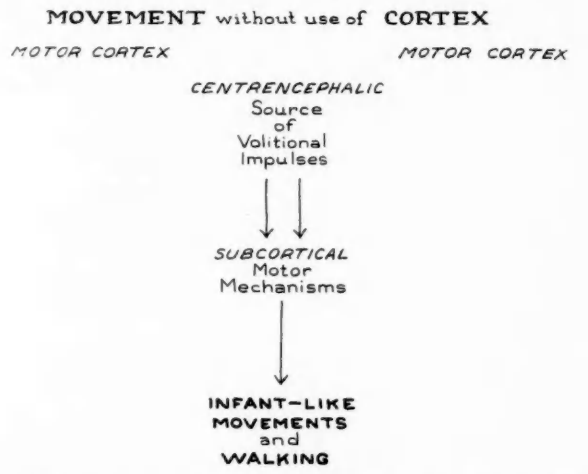

FIG. 6.—Hypothetical diagram of the course of nerve impulses producing voluntary action without employment of motor cortex.

for movement in the case of an adult deprived of precentral gyrus and also in the case of a normal infant as well.

On the other hand, when a normal, conscious adult lies on the operating table and it becomes necessary to stimulate the Rolandic motor (precentral) convolution with a gentle electrical current, movements are produced. Curiously enough, these are the movements, described above,

[1]Kennard (1940) has shown that the motor cortex may be removed from the infant chimpanzee with very little subsequent defect of function until the time comes for skilled hand movements.

of which the baby is capable at birth and approximately those of which the adult, who has lost his precentral gyrus and recovered from the initial "shock" is capable.

It seems difficult, on first consideration, to explain how stimulation of the normal precentral gyrus can produce the same type of movement as that which the adult, without a gyrus, can produce voluntarily, unless there is actually another neurone mechanism capable of carrying out these infant-like movements. One would have to assume that when the normal precentral gyrus is activated it has a control over this second mechanism, as suggested by the lines to "subcortical motor mechanisms" in fig. 7, but that, in the absence of the precentral gyrus, there is voluntary control of this mechanism via other neurone pathways which do not pass through the Rolandic cortex (suggested by the broken lines in fig. 7).

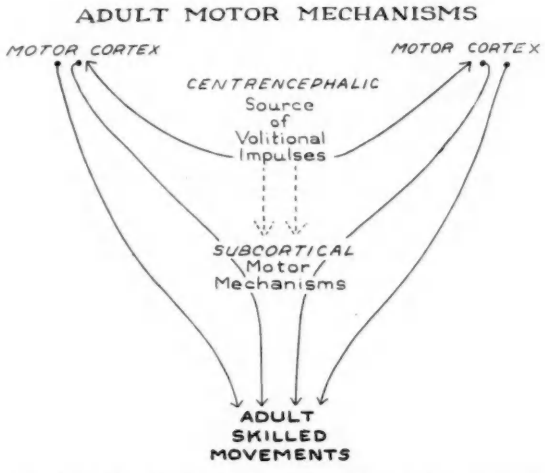

FIG. 7.—Hypothetical diagram of the stream of volitional nerve impulses from the centrencephalic area to each Rolandic motor cortex and from there to subcortical motor mechanisms and peripheral bulbo-spinal motor areas.

It is obvious that there are many motor mechanisms within the central nervous system that may be controlled by stimulation of the cerebral cortex although the effective neurone mechanism cannot be said to reside there. For example, respiration is controlled for the purposes of vocalization in four areas of the human cortex, the precentral gyrus of each side, and the supplementary motor area on each side as shown in fig. 8.

When certain parts of the lower Rolandic motor strip are activated, movements, ordinarily involved in mastication and swallowing (fig. 8), may be produced while respiration is simultaneously inhibited. Conjugate

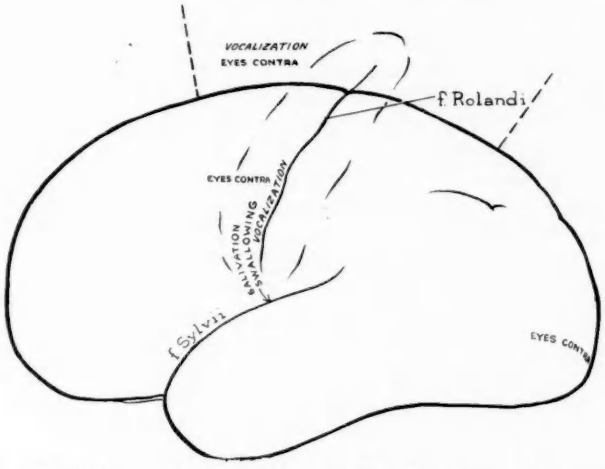

FIG. 8.—Cortical areas from which certain subcortical motor mechanisms can be controlled by electrical stimulation. The respiratory mechanism is also controlled during production of vocalization and swallowing.

turning of the eyes, with opening of the eyelids, may likewise be produced from various areas of the cortex: (1) the so-called motor eye field that, in man, is situated on the precentral gyrus and just anterior to it; (2) the occipital lobe; (3) the supplementary motor area (*see* fig. 8). The turning involved in this movement is usually away from the hemisphere where the stimulus is being applied.

However, when the cortex of an animal is removed completely the "preparation" may still chew and swallow. It breathes and turns its eyes in a co-ordinated manner. One may assume that man would do the same if he were to lose his cortex completely.

Vocalization control seems to find its first cortical representation in man. In animals, it is wholly or almost wholly subcortical to judge by the results of electrical stimulation. This control by the cortex is doubtless one of the inborn mechanisms that makes speech possible.

When any one of the four cortical vocalization areas is stimulated in man the result is roughly the same, regardless of side. When such an area is stimulated, the conscious patient carries out the following complicated set of movements, quite against his own will.

His mouth opens, the throat and larynx are held fixed, while diaphragm and abdominal muscles contract and force a stream of air through the larynx, making a vowel sound. If the stimulating electrode is held in place, this continues until it is interrupted by his taking a breath, after which he vocalizes again. (The cortical control over respiration seems to have been lost until the inspiration is completed.) These subcortical

mechanisms are probably the same as those which the child employs when he comes into the world with a vocalization of protest.

Thus it would appear that each of the relatively expert and complicated motor performances, that can be produced by electrical stimulation of the cortex, may be the result of cortical activation of a subcortical mechanism.

If the cortical motor system is to be utilized for the purposes of speaking, it is quite obvious that it must have easy control over articulation, but also over this vocalization mechanism and at least temporary control over breathing and swallowing.

It would seem that the awkward gross movements produced by stimulation of the hand, tongue and leg areas of the precentral gyrus give no more than an indication of the peripheral connexions of those portions of the gyrus. There is no suggestion that the acquired skills which are at the disposal of man have any form of true representation there.

Skilled movements of hands and feet, however, are only possible when the precentral gyrus is intact. The normal adult can carry out skilled acts with the right hand, for example, only when the hand area of the left precentral gyrus is intact. We may assume, therefore, that when he is carrying out such acts he utilizes the hand area of the precentral gyrus together with other distant or subcortical ganglionic mechanisms that can also be controlled through the precentral gyrus.

The diagram in fig. 7 suggests that under normal conditions volitional impulses arising in the centrencephalic area pass outward to the motor cortex and through it to the bulbospinal centres but also to the subcortical motor mechanisms. The dotted lines indicate that there is, as well, an additional pathway for voluntary control of the subcortical mechanisms and the bulbospinal centres at least when the cortex is not functioning.[1]

Discussion of the Function of the Precentral Gyrus

In the interests of definition and clear thinking, Walshe (1947) has belaboured the point of view that the human "pyramidal system, of

[1]When the right precentral gyrus has been destroyed in man some observers would assume that the continuing, though limited, voluntary control of the paretic extremities is due to the ipsilateral influence of the remaining precentral gyrus. It is impossible to deny that this may be the case at least to some extent. But electrical stimulation of the precentral gyrus of man practically never results in movement of the ipsilateral hand or foot.

The operation of hemispherectomy, better called hemicorticectomy, which leaves intact only the basal ganglia and brain-stem of one hemisphere, allows the patient to preserve motor function in the limbs of the opposite side about equal to that of the patient who has been deprived of his precentral gyrus alone. Lesions, that include the basal ganglia as well, seem to result in a more severe disability. The varying degree of spasticity that limits voluntary movement is another element to be considered, an element ignored in this discussion.

itself, initiates nothing, and to speak of it as responsible for this or for that category of movements is to ignore the source and motive power of its activities."

Then he continued as follows: "Willed movement is activated . . . by controlling cortical afferent patterns of excitation."

This is excellent, provided it is understood that the controlling impulses do not come across the cortex. They must come from a subcortical complex upon which the cortical afferents have already converged from both hemispheres.

It is not the left occipital lobe which guides the right hand by means of transcortical association tracts to the precentral gyrus. The right hand is propelled by a stream of impulses that comes to it, through precentral gyrus and spinal cord, from the zone of central integration (fig. 3). Each occipital lobe must contribute its hemianopic visual information to a centrencephalic system. Other currents of afferent impulses, particularly auditory and tactile, likewise pass through their cortical way-stations and on into the same system.

Take as an example the following situation:

Suppose a man's precentral gyrus has been removed and the postcentral gyrus for the hand preserved. The contralateral hand is paralysed but he continues to have accurate tactile information from the hand. He may use this information to guide the movement of the other, the normal hand.

It would appear, therefore, that even the postcentral gyrus sends the essential portion of the stream of sensory impulses, that reaches it, inward to the central integrating system. Transcortical connexions must serve some useful function but, at all events, this function is not essential for voluntary action.

I do not mean to suggest that when all forms of afferent sensory impulses reach the higher brain-stem, and when the records of past experience are likewise made available in the form of nervous impulse, that the resultant willed action follows as an automatic reflex. In my opinion, and this can be no more than an opinion, voluntary activity is not to be explained as an exclusively automatic phenomenon.

Consciousness is made possible by integration of the mechanisms of the cortex with those of the centrencephalic system. Consciousness does not vanish as the result of large destructions of cortex even when this includes that of the whole hemisphere[1]. But it does seem to vanish when there is direct interference with the function of the higher brain-stem. This has been pointed out by other neurosurgeons: Cairns, Jefferson, Dandy, as well as by Penfield.

What is the nature of consciousness? What happens when the inte-

[1]There is no clinical evidence, that I am aware of, to show what would happen to a man who had lost the cortex of both hemispheres without deeper injury.

grations of nerve impulses are translated into the phenomena of the mind? And, conversely, how is it that conscious decision can express itself in a patterned stream of efferent nerve impulses?

These questions do press themselves upon us for answer. They bring clinical physiologists face to face with psychologists and the religious philosophers in what may be called a common perplexity.

For the moment it is enough for us to consider the evidence, some of which has been presented, that there is an emerging current of nerve impulses that plays upon the precentral gyrus, and no doubt upon other ganglionic motor areas, during voluntary activity. Specific movements and skills do not depend upon origination of nerve impulses in the cortical motor gyrus. The "motive power of its activities" comes from elsewhere.

The Centrencephalic Integrating System

Arguments in regard to this must be based upon inference (Penfield, 1938, 1952*a* and *b*), although much recent work on the intralaminar and the reticular systems describes a wealth of to-and-fro connexions between this area and the cortex (e.g. Magoun, 1952; Jasper, 1952; *see* Penfield and Jasper, 1954).

I have used the word centrencephalic for hypothetical purposes, as mentioned above, to designate that neurone system which has been shown (or which may be shown in the future) to have symmetrical connexions with the two hemispheres and with the cerebrospinal axis; connexions which make possible integration of the total activity of the central nervous system.

We know that the general location of the centrencephalic system must be in certain portions of diencephalon, mid-brain and pons. The concept is a useful one but the general idea is not original. Sir Charles Sherrington spent a lifetime working out mechanisms which form a part of the integration of nervous impulses within the central nervous system. Hughling's Jackson maintained that the clinical evidence pointed to a "highest level" of neural integration somewhere in the brain. He even suggested that the location of this "level" might be in the frontal lobes.

The clinical evidence that such an area does exist is as strong today as it was in Jackson's time but present evidence throws new light on the general location of those neurone circuits in which the essential portion of the integration must take place. The centrencephalic system (never to be called centrencephalon), although it includes this "essential portion," functions together with, or employs the cortical areas.

For those who would discard the expression "highest level" because, as they point out with reason, a literal interpretation of the words would be misleading, another expression may be substituted, such as the area of final integration, or the central integrating system.

From the point of view of this present writing, the highest level of

integration might be described as that area of the central nervous system in which the final integration of nerve impulses takes place and the efferent stream of voluntary motor impulses is generated.

General Discussion

What, then, is the function of the precentral gyrus? Its function is to transmit, and no doubt transmute, the impulses which reach it from the central integrating system. This gyrus is a way-station in the stream of volitional impulses[1].

The precentral gyrus is divisible into a series of segments, the sequence of which is invariably the same (fig. 3). The nature of this sequence is determined by the peripheral connexions of the gyrus. In this sense only, we may say that movement of different portions of the body are represented there. In addition to that, certain subcortical mechanisms are represented there also, such as vocalizing, swallowing, conjugate eye movements.

Electrical stimulation of the motor cortex gives a true indication of what each portion of the gyrus may be used for. It does not use the gyrus as it is employed by the stream of voluntary impulses. That is self-evident.

Thus we know that one portion can be used to start and stop a vocalizing mechanism. Another part may be used to produce movement of the foot or fingers. The electrode cannot produce vocalization in the foot area nor vice versa. And I suspect that during voluntary action the stream of impulses that plays upon the precentral gyrus can produce foot movement and nothing else from the foot area.

It is with this understanding that motor maps of the cerebral cortex, such as those shown in figs. 1 and 3, are drawn and if a homunculus is used it is no more than an aid to memory. It serves the purpose of a pneumonic to recall the peripheral connexions of each portion of the gyrus. If this is understood, misunderstanding of the meaning of "representation" of movement may be avoided.

Speech might be considered the most important form of man's voluntary activity. Certainly it is one that we do not share with other mammals, one that requires elaborate integration before the movements of articulation and respiration involved in the act can be initiated.

Articulation and vocalization can be controlled through the lower portion of the Rolandic motor strip, to judge by the results of electrical stimulation. This portion of the motor apparatus can be excised completely

[1]It seems fair to suggest here that other subdivisions of the cerebral cortex play roles that contribute to the perfect total functioning of the brain, each in its own way. Certain sensory areas are afferent way-stations in the current of nerve impulses from periphery to the target of each in the centrencephalic system. Other areas provide the records of previous experience as needed. Still other areas are probably elaborative in fields of movement, sensation and thought.

without interference with the ideational mechanisms of speech and without aphasia even in the dominant hemisphere. It has been necessary to perform this ablation more than once.

But such removal does produce a severe anarthria or defective articulation. This gradually improves after operation. It seems likely that such a patient is able to speak by employment of the cortical motor mechanism of the other hemisphere.

Whether man would be able to speak at all if the articulation and vocalization areas of both Rolandic regions were removed without other injury to the brain is not known. One may be tempted to believe that the motor mechanism of speech, like the delicate skills of the hand, would be permanently impossible without the motor cortex. But this belief cannot be finally verified.

Summary

In conclusion, the precentral gyrus can be employed in the performance of skilled voluntary acts even when it has been cut off from surrounding transcortical connexions.

During voluntary dexterous movement of the right hand the resting rhythm of brain waves disappears in the arm area of the pre- and postcentral gyri but not in other parts of the Rolandic strip and not on the cortex anterior and posterior to the arm area. It disappears also when the command is given to prepare for movement of the hand. These electrographic observations are consistent with the belief that a subcortico-cortical stream of nerve impulses is directed toward that portion of the precentral gyrus during its employment in willed action.

Many of the final integrative processes that are prerequisite to planned voluntary action must take place in a central position within the brain, in what may be called the centrencephalic system.

The peripheral or efferent connexions of the different portions of the precentral gyrus are arranged in an invariable sequence from one end of the Rolandic strip to the other. These corticofugal connexions are of two kinds: (*a*) to the bulbar and spinal anterior horn areas, and (*b*) to subcortical motor mechanisms, of vocalization, swallowing, breathing, conjugate deviation of eyes, etc. Dexterous, voluntary movements of fingers and toes can only be carried out through the former connexions(*a*).

When the precentral gyrus has been removed, during early infancy when it seems likely that the precentral gyrus is not used, voluntary action is still possible. Under these conditions, dexterous employment of fingers and toes is not possible but skilful use of the subcortical motor mechanisms of swallowing vocalization, looking, etc., is still possible and gross movement of the extremities as well.

It seems likely that there may be an alternative pathway for directional voluntary impulses. When the motor cortex is not available it would seem that the subcortical motor mechanisms and, to a limited extent,

the bulbo-spinal anterior horn centres are controlled by streams of impulses originating in the centrencephalic system without making a detour to the precentral gyrus.

It must remain a matter of speculation as to what use may be made of the direct, extracortical pathway of voluntary control, under normal conditions of adult life.

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EFFECTS OF ALTERING THE PARAMETERS OF ELECTRICAL STIMULATING CURRENTS UPON MOTOR RESPONSES FROM THE PRECENTRAL GYRUS OF *MACACA MULATTA*

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INTRODUCTION

DURING the past century clinical studies, with ablation and electrical stimulation experiments, have outlined in its broad aspects the topographical representation of movement in the somatic motor area of the cerebral cortex of man and experimental animals. The complexity of the organizational plan in its finer details, however, has resulted in a continuing controversy as to the way in which the brain uses this neuronal motor apparatus to carry out cortically induced movements, experimental or volitional (Walshe, 1942, 1943, 1947*a*, 1947*b*; Clark, 1948; Murphy and Gellhorn, 1945*a*; Gellhorn, 1950). Stimulation studies in particular have provided much information regarding the properties of the motor cortex in this respect, especially as refinements in the stimulating currents have become available.

Evidence has been accumulating that the characteristics of the stimulating current (frequency, wave form, and pulse duration), as well as its intensity, are of importance in determining the response elicited when the electrode is applied to nervous tissue. Studies by Wyss and Obrador (1937) emphasize the relation between the pulse duration of the stimulating current and the threshold for various types of movements produced by cortical stimulation. These authors also re-emphasize the fundamental principle that the shape of each single stimulus and the rate of stimulation should be variable independently from each other. Other reports have appeared presenting incidental observations which indicate that alteration of the frequency of the stimulating current may at times cause a change in the motor response elicited from the cerebral cortex (Boynton and Hines, 1933; Hines, 1940; Garol, 1942; Bailey and von Bonin, 1946; Sugar, Chusid and French, 1948). Detailed information is scant regarding the effect of altering various parameters of the stimulating current upon motor

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responses elicited from the precentral gyrus of primates (Cooper and Denny-Brown, 1927–28; Clark and Ward, 1948; Liddell and Phillips, 1950). This study is an attempt to add to these data by studying in the monkey the responses elicited from fixed points on the motor cortex with stimulating impulses of varying characteristics.

Materials and Methods

This report is based on the results of approximately 5,000 recorded stimulations carried out on 15 adolescent monkeys (*Macaca mulatta*). 10 of these animals had been subjected to craniotomy sixteen to eighteen days previously for temporary occlusion of the right middle cerebral artery in connexion with another series of experiments. These animals were stimulated on the left side (opposite to the side of occlusion) prior to sacrifice. One animal had had an alumina cream disc placed over the right occipital lobe and on the twenty-first post-operative day stimulation studies were carried out on the left side. The remaining 4 were healthy animals who had had no previous experimentation and had been observed for several weeks to insure their freedom from defect. All animals gave comparable responses.

Dial with urethane[1] (Ciba) was employed in most instances, 0·45 c.c./kilo, half given intraperitoneally and the remainder intramuscularly. Nembutal[2] 25 mg./kilo, was given occasionally, while in other instances ether was used.

The head of the animal was secured, the motor area of the cerebral cortex exposed and bipolar silver electrodes separated by a distance of 2–3 mm. at their tips were fixed to rest lightly on the posterior portion of the precentral gyrus. The electrode holder was securely clamped in place so that the electrodes did not shift their position on the brain. If the electrodes were inadvertently shifted, however slightly, a new point was considered established. The contralateral limbs were allowed to hang loosely in space and the cortically induced movements studied by direct visual observation. In a few instances, the skin of the extremity was removed and the exposed muscles observed directly.

Exciting impulses were provided by a square wave generator which provided an output of impulses with pulse durations of 0·1, 0·3, 1·0 and 3·0 msec. with frequency variable from 2 to 200 impulses per second. Pulse duration, frequency and voltage were independently variable. The wave shape, on oscillographic analysis, showed approximately a 20 per cent decline at the 3·0 msec. pulse durations.

Stimulations were made at one minute intervals as a rule, although longer and shorter intervals were used to exclude the possibility of changes in response being related to intervals between simuli. Stimulus duration, in general, was kept at a minimum in order to avoid after-discharge. A mechanical timer provided a stimulus duration of 1·2 seconds. In some experiments a Morse key was used instead, providing a hand keyed stimulus estimated to be 1–2 seconds in duration. At very slow frequencies, however, longer stimuli up to 30 to 40 seconds were occasionally used. Threshold intensities were used except when mapping the effect of progressive increase in voltage.

[1]The Dial with urethane was supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[2]The crystalline Nembutal sodium used in these experiments was kindly supplied by the Abbott Laboratories, North Chicago, Illinois.

Results

A. *Frequency of Exciting Impulses*

The results of altering the rate of repetitive square wave impulses applied to points chosen at random on the precentral gyrus can be considered from two points of view, quantitative and qualitative.

(1) *Quantitative.*—It was found that if voltage, liminal at a low rate of stimulation, is maintained constant, while the frequency is increased, the motor response becomes increasingly more vigorous and more complex. Thus a concomitant decrease in voltage is necessary, as frequency is increased, to allow study of isolated movement, and it is with these responses to threshold intensities of stimuli we have been mainly concerned.

Fig. 1 shows the graphic appearance of the relationships when frequency is plotted against threshold or near threshold voltage, at a point near the junction of "face" and "thumb" areas. Occasionally the curve may present a more flat appearance, and the shape has been found to depend upon many variables all of which have not yet been studied. Occasionally there was observed a slight decrease in the liminal voltage at frequencies of 75 or 100 per second as compared to 200, but this decrease was usually not more than 0·2 volt and was not constantly seen. Furthermore, spontaneous fluctuations in threshold voltage of this degree were frequent at all frequencies.

(2) *Qualitative.*—It is the qualitative relations, the character of the responses elicited at various frequencies, with which we have been primarily concerned in this study. At many of the points stimulated there appeared a repeatedly reproducible change of motor response directly attributable to alteration in frequency. This type of response was more readily apparent in a uniform environment, under well-regulated anæsthesia, and from points near the junction of primary areas of representation, or from those areas usually assumed to represent more proximal muscle groups of the extremities. For example, stimulation of a point in the "arm" area near its junction with the "face" area produced only thumb responses at voltages of threshold intensity when the frequency was below 30, and only lip responses at frequencies above 30 with voltage at or near threshold (fig. 1).

Higher in the "thumb" area high frequencies often produced movement involving more proximal muscle groups in the extremity, either alone or with thumb movement. In fig. 2 thumb movement occurred with frequencies from 2–30 impulses per second, while with frequencies from 60–150 impulses per second wrist extension occurred either alone or with thumb movement.

Still another type of change was noted (fig. 3) in which three separate movements were elicited involving progressively more proximal muscle groups as the frequency was increased. In this instance fifth finger movement was produced at low frequencies (2–30 per second), pronation

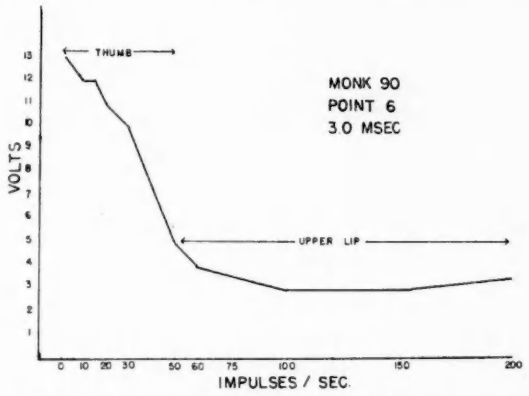

FIG. 1.—Effect of variation of frequency on threshold and type of motor response with electrode fixed in upper part of face area (3·0 msec. square wave).

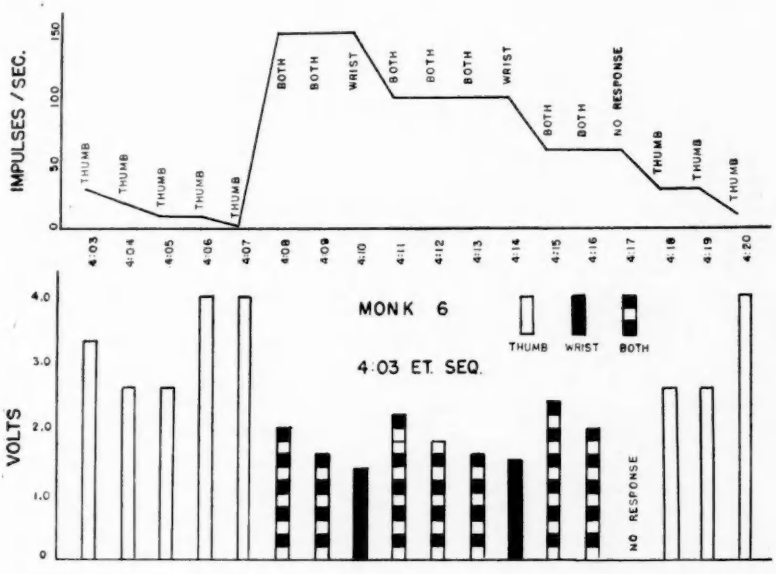

FIG. 2.—Effect of variation of frequency on type of motor response. Frequency of each of 18 consecutive stimulations indicated in top graph and voltage of these same stimulations in bottom graph (3·0 msec. square wave).

of the forearm at intermediate frequencies (60–75 per second) and shoulder movement at high frequencies (150 per second).

Essentially the same results were noted occasionally when the

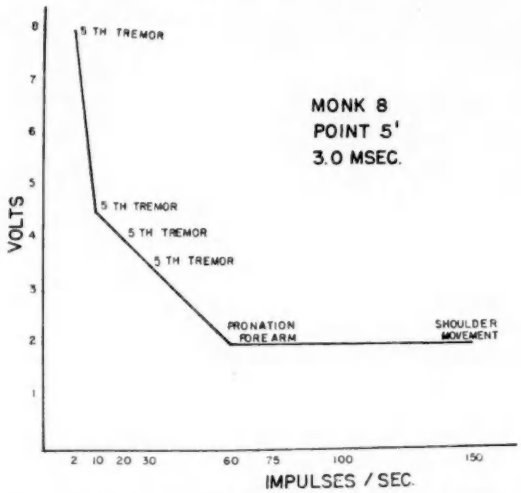

FIG. 3.—Effect of variation of frequency on threshold and type of motor response from point in upper part of arm area. Tremor of little finger occurred with low frequencies, pronation of forearm with intermediate frequencies and shoulder movement at high frequencies (3·0 msec. square wave).

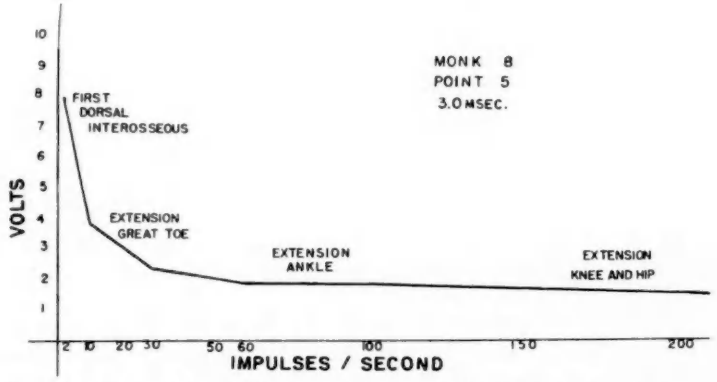

FIG. 4.—Effect of variation of frequency on threshold and type of motor response from point in leg area (3·0 msec. square wave).

electrodes were applied to the superior portion of the precentral gyrus, in the "leg" area (fig. 4).

At some points studied this tendency for the motor response to change with alteration in frequency was less marked than in others. For example, within the thumb area it was occasionally found that all frequencies repeatedly gave the same response. In many animals, however,

changing responses were produced from this area as well as from adjacent portions of the motor strip, the high frequencies serving to produce not a thumb movement, but extension of wrist or fingers or lip movement.

In three animals cortical maps were constructed of the somatic motor representation as determined by low frequency (2–10 per second), intermediate frequency (60 per second) and high frequency stimulation (200 per second). Stimulation of each point was carried out with these 3 frequencies and then the electrode moved to the next point (fig. 5).

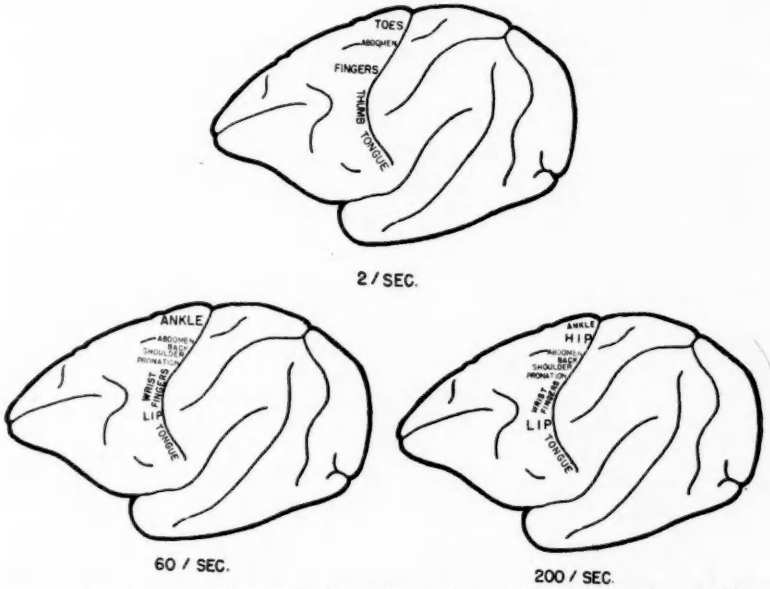

FIG. 5.—Diagram of points stimulated serially with frequencies of 2/sec., 60/sec. and 200/sec. (square waves of 3·0 msec. pulse duration) in monkey 12 (*see* Table I and fig. 6).

The threshold responses at these points and with these frequencies in one of the monkeys are shown in Table I. These are summarized in the diagrams in fig. 6. In each of the three animals the high-frequency map was characterized by a paucity of toe, thumb and finger movements, whereas the low-frequency map was predominantly made up of these responses and showed only rare responses of proximal muscle groups. The order of the motor sequence, however, was identical in each and the boundaries between the face, arm and leg subdivisions, as determined by these threshold stimulations, were almost identical.

It should also be pointed out that the type of movement at a given frequency was characteristic. At threshold voltage with frequencies above

TABLE I.—RESPONSES AT REPRESENTATIVE FREQUENCIES, ANIMAL NO. 12

Point	2–10	60	200
1	Abduct. 3, 4, 5 toes	Plantar flex. ankle	Plantar flex. ankle
2	Abduct. 3, 4, 5 toes	Inversion ankle	Hip
3	Nothing	Inversion ankle	Hip
4	Lower abdomen	Lower abdomen	Abdomen, hip
5	Nothing	Arch back, adduct. shoulder	Arch back, adduct. shoulder
6	Ext. 4, 5	Pronat. with slight ext. elbow	Adduction shoulder
7	Flex. 5	Ext. wrist	Pronation
8	Flex. 5	Ext. 3, 4, 5	Ext. finger
9	Ext. 2, 3, 4	Ext. wrist, fingers	Ext. wrist
10	Adduct. thumb	Ext. finger	Ext. wrist
11	Not done	Ext. wrist	Ext. wrist
12	Thumb	Flex. fingers	Flex. fingers
13	Thumb	Ext., flex. fingers	Flex. fingers
14	Right tongue	Tongue and lip	Tongue, lower lip
15	Tongue	Lower lip	Lower lip
16	Right tongue	Right tongue	Bilateral tongue
17	Right tongue	Right tongue	Medial tongue
18	Right tongue	Under surface tongue	Under surface tongue
19	Nothing seen	Bilateral posterior tongue	Under surface tongue

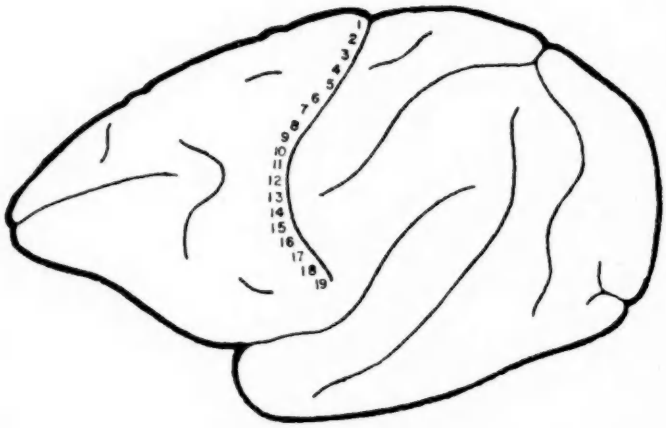

FIG. 6.—Diagrammatic representation of responses elicited in monkey 12 (*see* Table I and fig. 5).

30, a brief, smooth contraction was noted. Below 30 cycles, the movement was characteristically a tremor which followed the frequency of the stimulating impulses so far as could be determined by visual observation. The

frequency of 30 seemed to be critical in this regard since both a tremulous movement and a smooth movement often were observed simultaneously. Furthermore, the smooth movement, for example, pronation, was the one which had been seen at the higher range of the frequency scale; while the tremulous movement was the one which had been observed in pure form at the lowest extremity of the frequency scale, for example, extension of the thumb.

B. *Pulse Duration*

In regard to alteration in pulse duration these results also may be considered quantitatively and qualitatively. As might be expected, short pulses usually required a higher intensity of exciting current at a given frequency than longer pulse lengths under similar conditions. Usually the motor response at any given frequency was the same whether the pulse duration was 0·1, 0·3, 1·0 or 3·0 msec. Occasionally, however, a repeatable alteration of motor response occurred which seemed to correspond with alteration in pulse length. Such changes were present only at certain frequencies, thus altering the "cross over" point or frequency at which alteration of motor response occurred as the frequency range was explored. Fig. 7 shows responses over such a spectrum at near-threshold

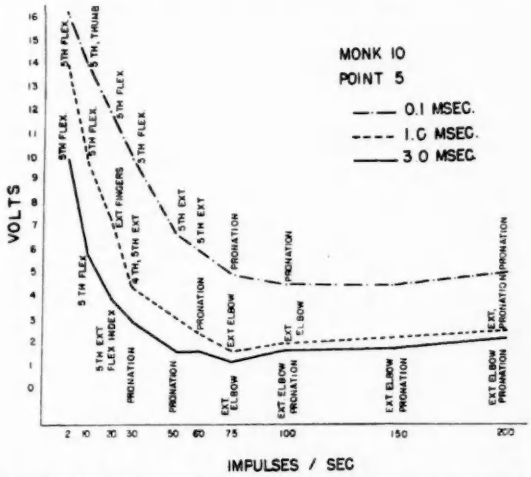

FIG. 7.—Effect of variation of frequency on threshold and motor responses from a point in the arm area using square wave impulses of 0·1, 1·0 and 3·0 msec. duration.

voltage and at three values of pulse duration, Although slight differences in the character of the responses are seen here at the higher frequencies, the most striking alteration is at the point where the movement at proximal joints (pronation) changes to the movement at distal joints

(finger movement). Note that this change occurs at 60 cycles with 0·1 msec., at 30 cycles with 1·0 msec., and at 20 cycles with 3·0 msec. Thus at 30 cycles per second pronation occurred with 3·0 msec. pulse duration, extension of 4th and 5th fingers with 1 msec. pulse duration, and flexion of the 5th finger with 0·1 msec. pulse duration.

C. *Intensity of Stimulating Currents*

We have observed on a few occasions, and almost invariably following motor after-discharge, that stimuli of voltage insufficient to produce active movement produced obvious relaxation of the tonic extremity. This observation confirms the electromyographic findings of Bosma and Gellhorn (1946) and the direct visual observations of Clark and Ward (1948). Since the majority of our experiments were carried out with the limb in the atonic state, however, opportunity for such observations was infrequent.

At the threshold voltage for any given frequency and pulse duration there occurred a simple discrete movement and, as has been frequently described, when this voltage was increased above that threshold the movement became stronger and usually additional movements were seen. Although this was the usual course of events, occasionally a real alteration in type of response occurred which seemed to be related only to the change in voltage. Fig. 8 shows such an unusual response where movement involving proximal muscles occurred at higher voltages and movement involving distal muscles at lower voltages. Alterations in voltage were

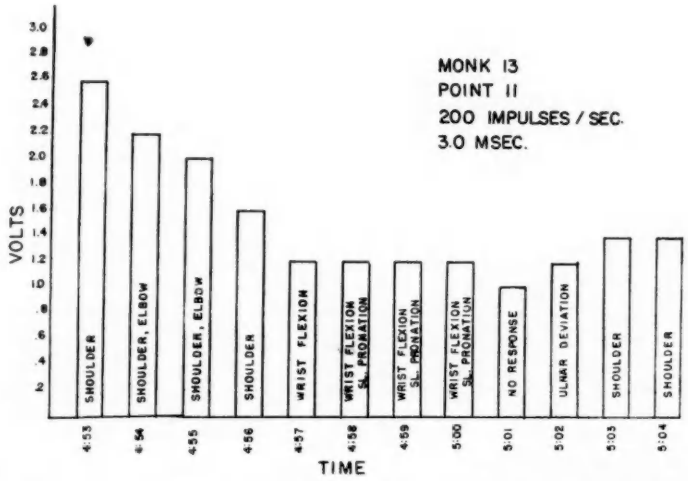

FIG. 8.—Change of type of motor response with change in intensity of stimulation of a point in upper part of the arm area (3·0 msec. square waves, 200 impulses per sec.).

particularly critical in the lower portion of the precentral gyrus. It was frequently noted, at various frequencies, that lateral deviation or retraction of the tongue could be changed to protrusion by increasing the voltage slightly (fig. 9).

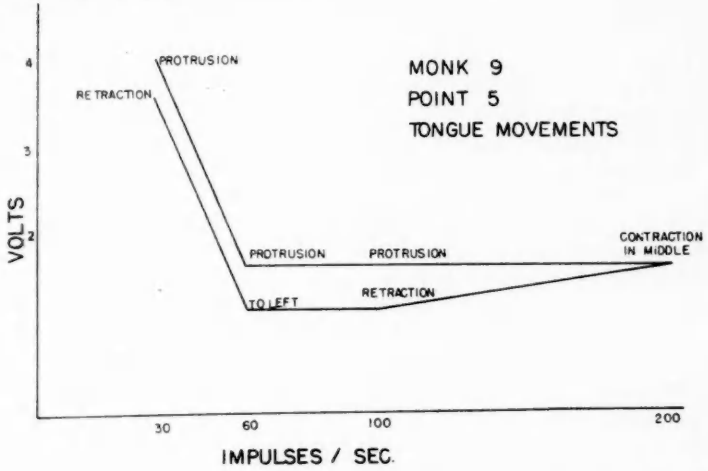

FIG. 9.—Change of type of tongue movement with change in intensity of stimulation of a point low in the face area (3·0 msec. square waves).

ANALYSIS OF MECHANISM

Several experiments were carried out to study a few of the many factors which might conceivably play a role in the production of the alteration of motor response with change in stimulation parameters. No definitive explanation of the process is yet possible but data bearing on some of its aspects have been collected.

A special study of the effect of the anæsthetic agent was made in three monkeys prepared with implanted electrodes. Silver-coated copper-ball electrodes were fixed in a lucite plug which was then screwed into a trephine opening in the skull so that the electrodes were in contact with the motor cortex. Stimulation studies were then carried out with the animal awake and under Dial, Nembutal and ether anæsthesia over a period of several days. The general pattern of contraction of distal muscles of the extremity with low frequencies and contraction of proximal muscles with high frequencies was found to occur with the animal awake as well as when anæsthetized with the above-named anæsthetic agents. Alteration of the plane of anæsthesia produced some changes in the responses, however, within this general pattern. This series of stimulations emphasized the necessity of avoiding extraneous sensory stimuli if reproducible responses were to be obtained. This was especially important

when the plane of anæsthesia was light and when the animal was awake. It was concluded that the anæsthetic agent was not a significant factor in these changes in responses to varying parameters of stimulation.

Because of the necessity of altering voltage concomitantly with frequency to produce a threshold response it was necessary to determine the possible effect of spread of current. Information in the literature relative to the spread of current during stimulation is limited. The most pertinent data are those of Murphy and Gellhorn (1945) who measured the spread of current on the cortex by direct recording, and found it to be a negligible factor in the explanation of the additional movements produced by increased stimulating voltage. A concentric electrode was used in several of our experiments and gave results similar to those obtained with the bipolar electrodes. In another experiment the cortex was incised between two points representing shoulder and thumb areas and a dielectric foil inserted into the incision. The selective shoulder and thumb responses previously elicited from the "shoulder" point with high and low frequencies respectively could then again be produced. Physical spread of current as well as spread via cortico-cortical connexions thus do not seem to be significant factors. More conclusive evidence was furnished by experiments in which stimulation of the white matter, after the removal of the overlying cortex by suction, produced the same change of motor response with varying frequencies as had been produced from the cortex before it was removed.

Thus it seems probable that integrative processes at subcortical and/or spinal levels are important in producing these frequency conditioned variations in motor response.

Stimulation of the brachial plexus and of the anterior roots resulted in constant motor responses with all frequencies and pulse durations. The ventral grey column of the spinal cord and the pyramidal tract have not been stimulated in this study. In this connexion it should be mentioned that Wyss (1947) found, in studying mammalian spinal reflexes, that stimulation of afferent cutaneous nerves produced flexor contraction and reciprocal extensor inhibition, whereas higher frequency stimulation of the same afferent fibres converted this effect into flexor inhibition with ensuing release. He found similar reversal of effect in studying vagal respiratory reflexes, low rates of stimuli being excitatory and higher rates being inhibitory, and postulated that this type of effect was mediated through the spinal internuncial pool.

Discussion

Movements induced by stimulation of the motor cortex must be the result of the local excitatory process produced in the cortex plus integrative action in the cortex and at various subcortical levels. Changes in various parameters of stimulation might influence one or more than one aspect of

this excitatory mechanism. The local effects of the stimulating current on the cortex have been studied more intensively than have the subcortical, bulbar and spinal integrative effects but even the former are poorly understood. Quantitative data are needed before the effects of changing frequency, pulse duration, wave shape and intensity can be properly assessed.

It has been assumed that the motor responses of stimulation of the precentral gyrus are due to activation of the pyramidal cells in the two lower cell layers of the cortex. Direct evidence of this was given by Dusser de Barenne (1934*b*) who found that following thermocoagulation of the three outer layers the threshold for unipolar faradic stimulation returned after two minutes to the same level as before, and further, that the motor response was the same. Further evidence favouring this hypothesis is given by the finding of Boynton and Hines (1933) that when a coated electrode was inserted down to the Betz cell layer the threshold was 1 volt, whereas stimulation on the surface had shown the threshold to be 3 volts.

There is some evidence to indicate that the superficial cellular layers also participate in the reaction to electrical stimulation. Adrian (1936) showed that stimulation with half or a third the intensity necessary to produce movement produced a negative potential for 2–4 mm. around the unipolar electrode, and demonstrated that this was the result of activation of superficial neuronal elements. The role played by these elements in the functional organization of the motor cortex is obscure. It is pertinent, however, to recall that Dusser de Barenne and Marshall (1931) showed there was a definite lowering of the threshold to faradic stimulation when 1 per cent procaine was painted in a circle around the point of stimulation and suggested that the procaine had effected a release of this point from inhibiting influence of surrounding cortex.

On attempt to go beyond these isolated bits of information when inquiring into the fundamental nature of the process by which an electrical current activates cortical neural mechanisms, a number of unanswered questions confront us. These include the relative importance of concomitant inhibitory influences set up by the stimulus (Bubnoff and Heidenhain, 1881; Cooper and Denny-Brown, 1927–28; Sherrington, 1947); the importance of certain quantitative considerations such as the percentage of neurones in a given area which are activated by the stimulus and the threshold of neurones of different types and sizes to the stimulating impulses; the importance of concomitant stimulation of nerve fibres traversing the area; and the importance of activation of circuits to subcortical nuclei (Dusser de Barenne, 1932).

In this study it should be noted that the muscle groups in the proximal portions of the extremities and in the trunk, which respond best to the higher repetitive rates, are those least extensively represented in the sensorimotor cortex and least affected by ablations of the motor area.

Conversely, the muscle groups in the distal portions of the extremities, which respond best to the lower frequencies, are represented most extensively in the sensorimotor cortex and are most severely paralysed by ablations of the motor cortex. Liddell and Phillips (1950) in a study published while this paper was in preparation, showed that in the baboon single square wave pulses of relatively high intensity produced flick-like movements of the opposite thumb, index and little fingers over a wide area, whereas at 50 cycles per second the same cortex produced the classical map of fine grain in which movements of all parts of the body are represented. Their results suggest that the frequency pattern presented in this report on the macaque is present in the baboon as well. It is of interest to note that Bourguignon (1923) found the chronaxie to be longer in the distal than in the proximal muscles and suggested that this would influence the characteristics of the electrical excitability of the cortical representation of these muscles.

McCulloch's (1944) statement—that increase in duration of the pulse, within physiological limits, will fire a larger proportion of the neuronal pool reached by a given voltage—may explain our finding an occasional instance of alteration of motor response with change of pulse duration. A fortuitous placement of the electrode in relation to the neuronal foci for the pertinent muscle groups, as postulated by Chang, Ruch and Ward (1947), might then permit such an alteration of response as varying proportions of the cells were activated.

The occasional appearance of change in type of response with alteration of voltage (fig. 8) is similar to that reported by Clark and Ward (1948) in their studies of stimulation of the motor cortex by implanted electrodes in the unanæsthetized monkey. They report occasional instances where "strong stimuli may produce a different pattern of response in which the movement elicited by weak stimuli does not occur or is completely masked by other stronger movements". In the example they cite, fanning of the toes occurred with 1 volt, while with 1·4 volts no fanning of the toes was seen but there was a violent flexion of knee and hip.

Recent studies suggest that subcortical structures may be of importance in relation to some of these variations in cortical response. Studies on the hypothalamus (Murphy and Gellhorn, 1945*b*), and on the brain-stem (Magoun and Rhines, 1947; Kempinski and Ward, 1950) indicate the necessity of considering the integrative action at these subcortical levels in analysing cortically induced movements. The effect of integrative action in the spinal cord in modifying such movements has been studied by Gellhorn and co-workers (1944, 1948, 1949) and has been invoked by Clark (1948) to harmonize the various theories proposed as to the mode of representation in the motor cortex.

Much new data along these lines will need to be accumulated before the motor apparatus in its various levels of integration can be viewed in proper perspective.

The importance of various parameters of stimulating current apparently varies from one cortical area to another, and from one species to another. In contrast to the results reported here for the precentral gyrus, the insula of the monkey yields the same type of autonomic response regardless of alteration of frequency, wave form or pulse duration (Hoffman and Rasmussen, 1953). Similarly, in man, sensory responses elicited from the postcentral gyrus are identical despite alteration of various parameters (Rasmussen and Cure). Preliminary results from a similar study of the precentral gyrus of man indicate that slight changes in motor response are produced at times by alteration of frequency of stimulating current, but in no instance were these changes of the degree we have found in the monkey (Rasmussen). However, Pool and Ransohoff (1949) on simultaneous bilateral stimulation of the anterior portion of the cingulate gyrus in man produced elevation in blood pressure in 8 of 12 patients (and a fall in one) with frequencies ranging from 15 to 60 cycles per second and, in one case, found that frequencies of 90 to 120 per second were ineffective. Chapman, Livingston and Livingston (1949), stimulating the orbital surface of the frontal lobes in patients undergoing frontal lobotomy under light pentothal anæsthesia, found that blood pressure and respiratory effects could be elicited with frequencies of 10–30 per second while slower and faster frequencies were usually ineffective.

Delgado and Livingston (1948) found that stimulation of one point on the cortex of sulcus presylvius in the dog with 60 cycles per second produced only slowing of respiration; 6 cycles per second caused a complete arrest with augmentation of the inspiratory position; 30 cycles per second caused augmentation of amplitude in both inspiratory and expiratory directions; and 180 cycles per second caused little or no effect.

It is in the cerebellum, however, that the frequency of the stimulating current seems to be most critical. Moruzzi (1950), for example, showed that stimulation of the inhibitory area of the anterior lobe of the cerebellum in the precollicular cat resulted in inhibition of rigidity on the ipsilateral side with frequencies of 50–300 per second, whereas at 2–10 per second an increase of rigidity was constantly seen.

This brief survey emphasizes the importance of determining experimentally for each part of the central nervous system the effect of varying the parameters of electrical stimulating impulses, and it also cautions one against extrapolating results from one animal species to another without experimental verification.

Summary

(1) Stimulation of fixed points on the motor cortex of anæsthetized and unanæsthetized monkeys was carried out with square wave impulses at frequencies of 2–200 per second and with pulse durations of 0·1 to 3·0 milliseconds.

(2) On stimulating the same point with threshold intensities, change in

frequency (under otherwise constant conditions) often produced an alteration in type of motor response, low frequencies (2–20 per second) producing movement involving distal muscle groups of the extremity, and higher frequencies (30–200 per second) producing movement involving only proximal muscle groups of the extremity. This type of response was found to occur most frequently near the borders between the primary subdivisions of the motor area, the face, arm and leg areas. In the centre of the thumb area a constant response to all frequencies was occasionally seen.

(3) Pulses of shorter duration usually required a higher voltage to produce a motor response than did pulses of longer duration. The response was usually the same for the various pulse durations in this range. Occasionally, however, changing the pulse duration produced a change in the type of motor response, the longer pulses favouring movements involving proximal muscle groups. This alteration of response usually occurred near that point in the frequency range where the distal type of response changed to the proximal type of response when the frequency range was explored.

(4) Increasing the intensity to above threshold voltage usually resulted in increasing vigour of the threshold response along with innervation of additional muscles. On occasion, however, suprathreshold voltage produced movement involving proximal muscle groups, whereas threshold voltage produced movement involving distal musculature of the extremity.

(5) Stimuli of apparently subthreshold intensity produced relaxation of the tonic extremity in some experiments.

(6) The frequency-conditioned change of motor response could be repeated after removal of the cortex just stimulated by repeating the stimulation procedure on the underlying white matter. This suggests that these alterations in motor response to stimulation of the motor cortex are due to integrative processes at subcortical and/or spinal cord levels.

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AN EXPERIMENTAL CRITIQUE OF THE EFFECTS OF ANTERIOR CINGULATE ABLATIONS IN MONKEY[1]

BY

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Recent use of anterior cingulate ablation in the treatment of mental illness makes imperative a reinvestigation of the consequences of such ablation in sub-human primates. The operation was introduced on the grounds that behavioural changes such as "loss of fear" and "social indifference" result from bilateral removal of the anterior cingulate in monkeys. This conclusion was based on three studies involving some 14 animals (Smith, 1944; Ward, 1948; Glees, Cole, Whitty and Cairns, 1950). The experiments which lead to these conclusions were relatively short-term (two or three months), and only two of the animals in question had been trained, i.e. tested before and after operation. Histological analysis of the lesions is adequately reported in only one of the studies based on six brains (Glees *et al.*, 1950). In the present series of experiments available neurophysiological, neurosurgical, and neuroanatomical techniques were used for elucidating the basic problem of functional localization in the cingulate and medial frontal cortex.

Frontal cortex may be divided into eugranular (granular) and dysgranular (incl. agranular) portions. Specific behavioural changes have previously been correlated with ablations of all dysgranular areas (precentral motor [Lashley, 1924; Fulton and Keller, 1932; Denny-Brown, 1952] and frontotemporal [Pribram and Bagshaw, 1953]) save those abutting the corpus callosum (cingulate). In addition, selective changes in behaviour follow removal of dorsolateral granular cortex (Pribram, Mishkin, Rosvold, and Kaplan, 1952). The present report is concerned with the remaining frontal cortex: the effects of bilateral lesions of cingulate areas *per se*, and the effects of a combination of such lesions and removal of the ventromedial frontal granular cortex. The effects of anterior cingulate ablation when added to excision of the precentral

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motor cortex are reported in another study (Berman, Robinson, and Pribram, 1951).

Materials and Methods

Subjects.—Fifteen rhesus monkeys were used in this study: 5 were unoperated controls and 10 were subjected to bilateral ablations of the anterior cingulate gyrus. In addition, serving as operated controls, were 2 spider monkeys with aluminum hydroxide implantations over the cingulate cortex, one mangabey with a total anterior frontal lobectomy, and two baboons, one with a medial, the other with a lateral frontal ablation.

Behavioural observations.—A transport cage was used to move the animal from individual living quarters to an air-conditioned, sound-proofed, darkened testing room. Here the cage was moved into a dimly illuminated enclosure and secured in place, facing an opaque screen which separated the animal from the testing apparatus. When the opaque screen was raised the animal was confronted with a sliding tray to which were attached two rectangular metal cups spaced 12 in. apart. Metal cup covers, 3 in. × 4 in., served as interchangeable stimulus plaques. The animal quickly learned to displace these plaques to obtain the concealed reward (peanut). A one-way vision screen was lowered, the tray pushed forward, and the animal was permitted to make a choice. Left and right cups were baited in random order. The non-correction technique was employed. No punishment, other than withholding reward, was given for errors. Thirty trials were presented daily until the criterion of 85 correct in 100 consecutive trials was achieved. At this time, the opaque screen was interposed for delays of 0, 5, and 10 seconds after baiting; a criterion of 85 correct in 100 consecutive trials was achieved at one delay interval before the next longer interval was administered.

A visual pattern discrimination test was administered in the same apparatus. Stimulus plaques were painted bright yellow; on one a "plus," on the other a "square" was painted in flat black. The cup bearing the plaque marked "plus" was baited behind the opaque screen, the screen raised, and the animal permitted to make a choice. The position of the plaques was shifted so that the reward was located in the two cups by random order. Non-correction technique, no punishment, was used. Criterion was 85 correct choices in 100 consecutive trials. Reaction to aperiodic withholding of reward after correct choice, once the discrimination had been learned, was also observed. Duration, in seconds, of avoidance of the five trials subsequent to withholding of reward was measured. Maximum time allowed to elapse between trials was 20 seconds.

Systematic observations of the animal's activity were recorded daily. These observations included kind and degree of (1) *motility:* running, jumping, walking into and out of the transport cage, pacing, circling, sitting in the transport cage preceding, during, and following the testing session; (2) *reactivity:* pouncing, slapping or biting the cage, attempts to escape, crouching, defæcation, piloerection; and (3) *vocalization:* screaming, barking, chattering. In addition, one animal was placed in an enclosed, illuminated and ventilated sound-proofed cage, where a record of its locomotor activity was made by means of an R.C.A. Capacity Operated Relay, grounded to the cage floor and to antennæ at both ends. Changes in the antenna capacity, caused by movement of the animal in the field between the antenna and ground, activated one of 24 counters every hour (Davis, 1951). Daily food intake and basal rectal temperature were also recorded for this animal.

Social behaviour was observed in a colony of six preadolescent males by recording techniques previously described (Tinklepaugh, 1942; Warden and Galt, 1943; Brody and Rosvold, 1952). A stable dominance hierarchy became established and was observed in relation to obtaining food (one peanut at a time) and with

respect to grooming behaviour. In addition, one adult male macaque was observed for a period of eighteen months living with a mature female and the resulting offspring.

Surgical procedures.—Under sodium amytal anæsthesia (0·6 c.c. 1 per cent soln. per kg. body wt.), a full osteoplastic calvarium flap was turned on the left temporal muscle. The dura was opened in a cruciate manner over the left frontal lobe. Bridging veins to the sagittal sinus were coagulated and the hemisphere retracted to expose its medial surface. A variable extent of the cortex of the anterior cingulate gyrus, precallosal and subcallosal areas, and of the medial frontal lobe was resected subpially with an 18-gauge needle sucker. A comparable excision was attempted on the right, the approach being through the falx. For the control operations, essentially the same steps were taken except that in two animals aluminium hydroxide implantations in small silver discs (4 on each anterior cingulate gyrus) were substituted for the ablations. The total lobectomy and the lateral frontal removals necessitated opening of the dura bilaterally. All subjects were observed for a minimum of three months after operation.

Anatomical methods.—Under a lethal dose of barbiturate, the animals were perfused with normal saline followed by a 10 per cent solution of formaldehyde. The brains were removed, placed in several washings of 10 per cent formaldehyde, then transferred to increasing concentrations of alcohol for dehydration. Imbedding proceeded first with 2 per cent nitrocellulose, then with 10 per cent celloidin. Serial sections at 25 mu were made, every 20th section stained with analine thionin. Tracings of every fourth stained section (2 mm. intersection intervals) were used to plot the outline of the hemisphere, the principal fissures, and the lesion on graph paper. In addition, thalamic degeneration was analysed and plotted. Criterion of degeneration in the anterior nuclei was cell loss.

Results

Behavioural results.—Six of the animals were trained both pre- and post-operatively on the visual discrimination and delayed response procedures. With one exception, all animals took fewer trials on either test to reach criterion post-operatively than pre-operatively (Table I). The

Table I

	Discrimination		*Delay*	
	Pre	*Post*	*Pre*	*Post*
Cin. 1	120	80	820	360
Cin. 2	400	60	600	150
Cin. 3	115	74	215	150
Cin. 4	240	140	345	180
VM	280	120	380	230
DL	120	100	240	500F

Number of trials includes criterion trials.

Results of performance on visual pattern discrimination (left) and delayed reaction tests. Pre = pre-operative, Post = post-operative scores of number of trials taken to reach criterion of 85 per cent on 100 consecutive trials. Cin. = cingulate ablation; VM = ventromedial frontal ablation; DL = dorsolateral frontal ablation. Note that all post-operative scores are lower than pre-operative except for that of DL on the delayed reaction test.

exception had received an ablation, not of the cingulate and medial frontal cortex as had the others, but of the dorsolateral frontal granular areas. These results confirm those of a more extensive study reported elsewhere (Pribram, Mishkin, Rosvold, and Kaplan, 1952).

When a reward is aperiodically withheld from a subject following correct choice in an established discrimination, one of two types of behaviour results. Either the animal ignores the episode or it shows a gross avoidance reaction characterized by retreating to the rear of the testing cage, pacing, vocalizing, or pouncing. Avoidance of subsequent trials varies from a short delay in the response to a complete refusal to test further. Of a group of 4 macaques, 2 showed the former reaction, 2 the latter. These latter animals were subjected to ablation of the anterior cingulate cortex. A definite decrease in the duration of the avoidance behaviour resulted (Table II). However, as can be seen from the table,

TABLE II.—FRUSTRATION

	Pre-op.	*Post-op.*
Cin. 1	—	23 sec.
Cin. 3	—	12 sec.
Cin. 5	42 sec.	3 sec.
Cin. 6	22 sec.	0·2 sec.
N 1	0·2 sec.	—
N 2	0·2 sec.	—
Lob	—	2 sec.
VM	90 sec.	53 sec.
DL	62 sec.	18 sec.

Results of performance on "frustration" trials. Seconds avoidance of trials subsequent to "frustration trial" indicated pre- and post-operatively. Cin. = cingulate ablations; N = normal; Lob = frontal lobotomy; VM = ventromedial; and DL = dorsolateral frontal ablations. Note that all frontal operations shorten the duration of the avoidance reactions.

this effect is also noted when dorsolateral frontal granular areas are ablated.

No consistent changes in the systematically observed ratings of activity (motility, reactivity, vocalization) were obtained when the pre- and post-operative scores of the tested macaques were compared. Nor was there any dramatic change in the activity measured in the activity cage. In contrast to the changes following frontotemporal ablations, no long-term changes in food intake or basal rectal temperature followed resection of the cingulate gyrus (Pribram and Bagshaw, 1953).

The social structure of a colony of immature male rhesus monkeys was unaltered by interposing extensive anterior cingulate ablations into the situation. No effect on dominance rating with respect to feeding or grooming behaviour could be observed when either the most dominant or the next to the most submissive animal in the group was operated upon

TABLE III.—SOCIAL COLONY

Pre-operative period	*Operative period*	*Post-operative period*
Cin. 7	—	Cin. 7
N 3	N 3	N 3
N 4	N 4	N 4
Cin. 8	—	Cin. 8
N 5	N 5	N 5

Dominance hierarchy is recorded from top down. Cin. = cingulate ablations; N = normal. Note no change in the structuring of the social colony subsequent to the surgical procedures performed on Cin. 7 and Cin. 8.

(Table III). These results are in marked contrast to those obtained in similar social situations following lobotomy (Brody and Rosvold, 1952) or anteromedial temporal lobectomy (Rosvold, Mirsky, and Pribram. In Press).

Lest the technique of observing the structure of a colony of immature animals of the same sex be insensitive to more subtle changes in social behaviour, a mature male was observed briefly (forty-eight hours) in relation to another adult male and also an adult female. He was then subjected to bilateral anterior cingulectomy. After two weeks he was again observed for forty-eight hours in relation to the other mature male and then placed with the mature female for eighteen months. No dramatic change in behaviour was noted toward the other male except that there appeared to be somewhat less prolonged fighting over food, the cingulectomized animal being dominant as before operation. In his relations with the female, the operated animal behaved within normal limits in all respects. A mutually protective relationship was established; the female was dominant in food situations as she had been prior to operation; grooming and sex relations were observed neither more nor less frequently than prior to operation. A baby macaque resulted from the relationship and the operated subject behaved in a most protective manner toward his family at all times: e.g. when the group was threatened with a stick, the operate would grimace, pounce, rattle the cage, and place himself between the threat and his family.

Neurological results.—The effects of ablation of the anterior cingulate cortex might be ascribed to the production of scar around the margin of the excision. In order to test the effects of such lesions 2 spider monkeys were given aluminium hydroxide cream implantations over the cingulate cortex. Weekly electrographic (animals narcotized with Nembutal) and daily behavioural observations were made. No consistent changes were noted: specifically, we observed no *petit mal*-type seizures, *grand mal* seizures, ataxia, weakness, or altered social behaviour with respect to each other or toward the experimenter. For a period of two weeks, approximately one month post-operatively, abnormal spikes referable to

the right central scalp lead were recorded from one of these monkeys. This finding disappeared, however, and no other electrographic abnormalities were noted.

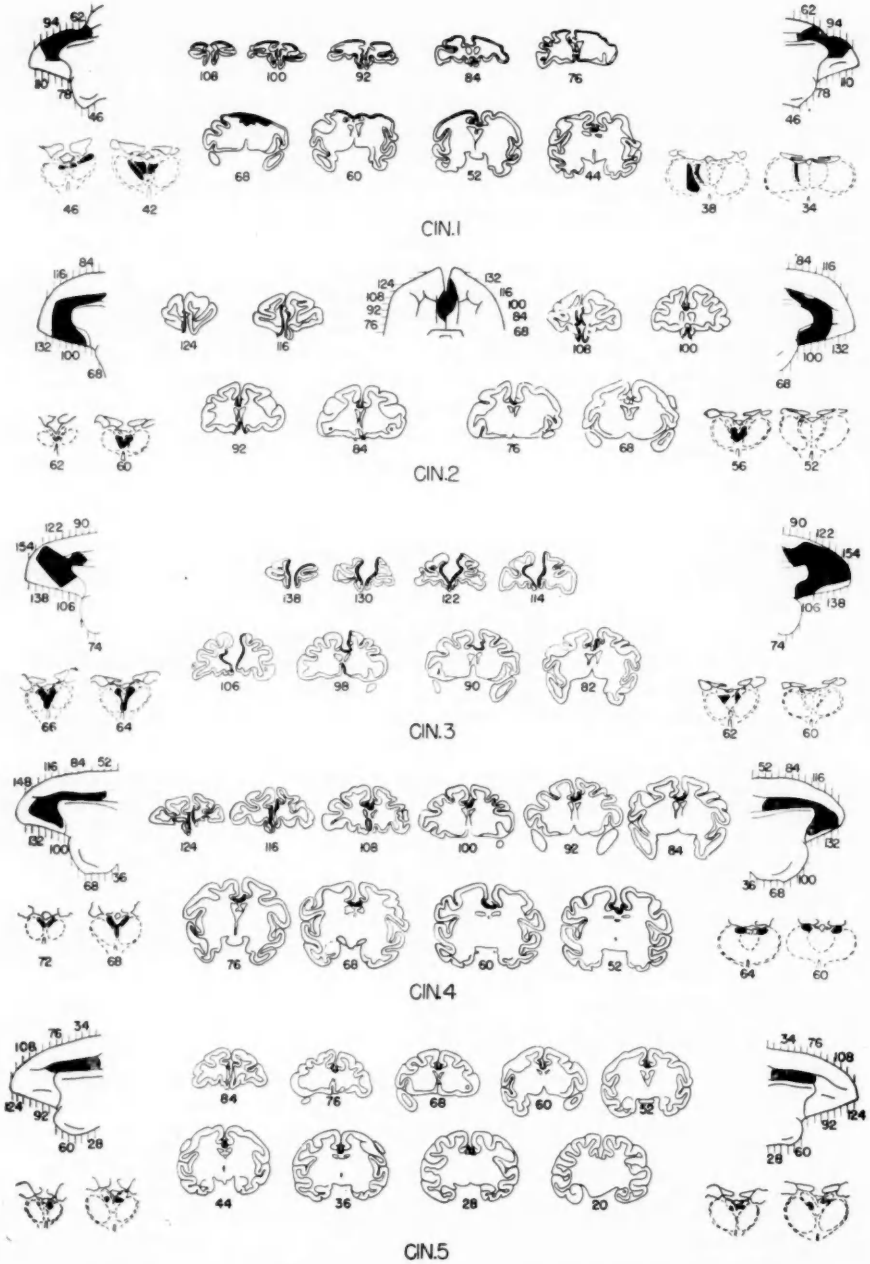
The anatomical findings are presented by means of serial reconstructions of the hemispheres with representative cross sections through resected portions (figs. 1 and 2). Retrograde degeneration in the thalamus associated with the ablations is shown diagrammatically. Whenever the resection is limited to the anterior cingulate gyrus above the corpus callosum, there is degeneration in a strip located at the junction of the n. anterior medialis and n. anterior ventralis (Cin. 5, Cin. 8, Cin. 9). More extensive invasion of the medial frontal cortex anterior to the corpus callosum leads to massive degeneration in the central portion of the n. anterior medialis (Cin. 1, 2, 3, 4, 6, 7, 10). Involvement of the subcallosal areas results in degeneration of the medial and ventral portions of this nucleus and of the n. paratenialis (Cin. 2, 3, 4, 6). Where degeneration appears in the n. anterior ventralis, the ablation extends far posteriorly in the cingulate gyrus (Cin. 4, 6, 10) or there is invasion of fibres under the anterior cingulate cortex (Cin. 2, 3, 7).

Discussion

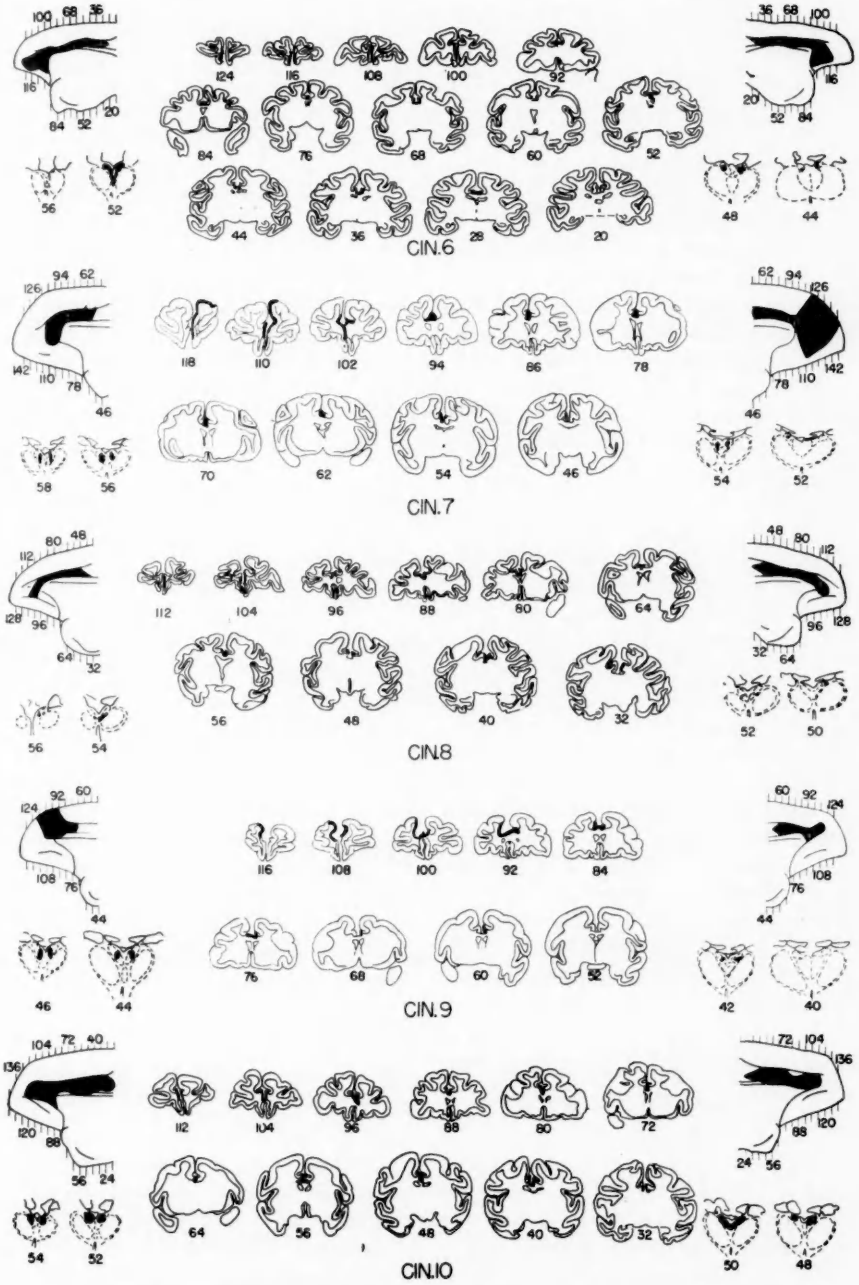
The results of these experiments indicate that resection of the cortex of the anterior cingulate gyrus, and of the pre- and subcallosal and medial frontal areas as well, does not lead to the profound and prolonged alterations in behaviour reported in earlier studies. Rather, when ablation is limited to cortex, the effects are transient, apparently minimal, and difficult to appraise. This finding is in essential agreement with that of Glees, Cole, Whitty and Cairns (1950). Since no anatomical verification appears with other reports, discrepancies with respect to the more dramatic findings cannot be resolved.

There has been considerable variability in the reported effect of frontal lesions on "emotional" behaviour of primates. On the basis of the observation that following leukotomy avoidance reactions in man are not minimized (e.g. pain threshold is unaltered) but that suffering and anxiety are reduced, we devised a measure of the duration of an avoidance reaction[1]. This measure was sensitive to the effect of anterior cingulate and medial frontal ablations. However, an effect of equal magnitude was recorded to follow lateral frontal removals. Since such lesions result

[1] Since this is a critique, certain limitations of this test technique should be mentioned. It is known that the scheduling of aperiodic reinforcement is a most important variable in determining the rate of response. No information is available on the effect of aperiodic presentation of aversive stimuli—either in determining conditioned avoidance behaviour or in extinction. Thus, the crude technique used in the present experiments must be validated with better controlled interval reinforcement and aversive scheduling. The data are reported in the hope of stirring interest in this problem.



FIGS. 1 and 2.—Cross sections and reconstructions of bilateral anterior cingulectomies and the resultant retrograde thalamic degeneration. Cin. = cingulate.



Lesion and degeneration indicated in black. Thalamus in dashed lines. Numbers refer to placement in series of cross sections.

in additional impairment (delayed response-type problems) the medial procedure appears the more selective.

The anatomical observations confirm and amplify those of previous investigations (Mettler, 1947; Rose and Woolsey, 1948; Lashley, 1941; Walker, 1938). Taken together with the findings of the present experiments, orderly arrangement of the projection of the anterior nuclei to the cortex becomes apparent. An axis drawn through the main nucleus from a dorsolateral to a ventromedial position projects to the cortex along a postero-antero-ventral arc paralleling the corpus callosum above and bending around its genu. In addition, the evidence suggests that the more medial portions of the nucleus project to the more hilar portions of the cortex, whereas no differentiation of the projection of the antero-posterior axis of the nucleus is apparent. These findings of an orderly arrangement of thalamocortical projection from the anterior nuclei may now be added to those described for the lateral geniculate, pulvinar, and mediodorsal nuclei (Lashley, 1941; Chow, 1950; Pribram, Chow and Semmes, 1953).

The anatomical findings are also of interest with respect to current theories of the neuro-anatomical correlates of emotions. The restricted connexions of the anterior cingulate gyrus *per se* with the anterior thalamic nuclei, added to the findings (Reviewed by Pribram and Kruger) that apparently only the posterior portion of the hippocampus of monkey sends fibres to the mammillary bodies, warrant a re-examination of the much publicized "hippocampus-mammillary-anterior nucleus-cingulate-hippocampus" circuit. There is, no doubt, ample evidence that such connexions exist (Lorente de Nó, 1933, 1934; Clark and Boggon, 1933; Pribram and MacLean, 1953); that they serve functions not served by other multiple chain neuronal connexions remains to be shown. In view of the paucity of behavioural changes reported in this study, the absence of any reported change after complete bilateral hippocampectomy (Mishkin. In Press), and the absence of effect of electrical stimulation of the greater portion of the hippocampus in either the anæsthetized or ambulant animal (Kaada, Pribram, and Epstein, 1949; Andy and Akert, 1952), it seems premature to decide what rôle these structures have in determining behaviour—and to base therapy on such decision.

Summary

(1) Twenty monkeys, 12 with lesions of the anterior cingulate gyrus, were used to study the effects of bilateral anterior cingulectomy.

(2) Behavioural observations consisted of testing the performance of the animals on the delayed reaction problem, a visual discrimination problem, their reaction to a "frustrating" situation, and their social behaviour. Only with respect to the reaction to "frustration" was any change in behaviour induced by the cingulectomy. Shortened duration of

avoidance behaviour resulted from ablation of the anterior cingulate cortex. Although similar changes follow other frontal lesions, these are accompanied by additional impairment—viz. of performance of the delayed reaction type of problem. Thus, medial frontal and cingulate resections have been shown to shorten selectively the duration of avoidance.

(3) Anatomical observations with respect to the projection of the anterior thalamic nuclei are of interest. The more posterior the ablation of the cingulate gyrus extends, the more degeneration is found in the n. anterior ventralis. Resection restricted to the anterior portion of the cingulate gyrus results in degeneration limited to a strip at the junction of the n. anterior ventralis and the n. anterior medialis. Invasion of the medial frontal cortex anterior to the corpus callosum is associated with massive degeneration of the n. anterior medialis. The most ventral portions of this nucleus and the n. paratenialis degenerate when the subcallosal cortex is involved. These observations establish the fact that the projection of the anterior nuclei terminate in an orderly manner in the cingulate and medial frontal cortex. An axis through the anterior thalamic nuclei extending from the dorsolateral to the ventromedial positions projects to the cortex along a postero-antero-ventral arc paralleling the corpus callosum above and bending around its genu. In addition, the evidence suggests that the more medial portions of the nucleus project to the more hilar portions of the cortex. No differentiation of the projection of the antero-posterior axis of the nucleus is apparent.

ACKNOWLEDGMENTS

The present problem has been under study in the Laboratory of Physiology at Yale University and later in the new laboratory of one of us (K. H. P.) at the Institute of Living in Hartford, Connecticut, for a period of nearly four years. It should be recorded that the problem was first studied in collaboration with Dr. Robert B. Livingston but our early attempts at isolated removal of the cingulate failed owing to the fact that we had not at first overcome surgical difficulties. Training studies on some of the animals used were carried out by Drs. R. McDonnell, R. Dunsmore, R. Hughes and L. Porter, Messrs. W. Wilson and J. Barry, and Mrs. Muriel Bagshaw. Dr. Margaret Lennox assisted with EEG studies. We take this opportunity to express our gratitude for their participation.

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DELUSIONAL REDUPLICATION OF PARTS OF THE BODY

BY

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Introduction

The delusion of reduplication of parts of the body is a phenomenon occurring among patients with disease of the brain. Bechterev, in 1926, reported the case of a man with a left hemiplegia who, for several months, expressed the delusion that he had two left hands, three heads and six feet. Bechterev called the phenomenon "pseudopolymyelia" derived from Ostankov's (1904) term "pseudomelia paresthetica" referring to the sensation in phantom extremities. In 1930, Ehrenwald described a patient who, following a vascular accident with left hemiplegia, said that he had a "nestful of hands" in his bed. Subsequently, he maintained that he had two left hands which he designated as "old" and "new" and "good" and "bad." In 1934, Chlenov studied a patient who claimed he had two left ears and Shmarian (1934) observed a man with a left hemiplegia who maintained he had two left hands. Schenderov and Gamaleja (1935) published a detailed study of six cases of reduplication of body parts in patients having left hemiplegia with autopsy studies in three cases. They referred to the phenomenon as "pseudomelia" and suggested that their observations of six instances in a period of two years indicated that its occurrence was more common than had been supposed. Since then reports of cases with similar delusions have been made by Hoff and Pötzl (1935), Golant-Ratner (1937), Schaeffer (1942), Meerovich (1948), Critchley (1952), Arnold and Hoff (1953) and by Brock and Merwarth (1953).

The reported cases have been mainly those of patients with left hemiplegia and the reduplication has been related by most authors to anosognosia or denial of hemiplegia. The explanations of the phenomenon have paralleled the particular author's concept of anosognosia. Critchley (1951) has grouped both under parietal lobe syndromes. Bechterev considered reduplication to be simply a manifestation of "irritation" of

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sensory pathways. Other writers have considered reduplication and anosognosia to be a result of disruption of the "body scheme" in which the lesion destroys the particular area in the parietal lobe or its connexions where the image of that particular part of the body is represented.

The present study concerns 4 patients with delusions of reduplication of various portions of the body. The phenomenon will be evaluated from the standpoints of (1) functional localization in the nervous system, (2) alterations in perception, and (3) relation to other changes in behaviour, particularly other forms of reduplication and anosognosia.

Case 1.—A 57-year-old nurse was admitted to The Mount Sinai Hospital on April 30, 1952, with a history of anorexia and pain in the right lower chest of two to three months' duration. During this period there had been a 10 lb. weight loss. Examination revealed a slender, poorly developed woman. Her abdomen was diffusely tender, slightly distended and the liver edge could be palpated 4 cm. below the costal margin. Neurological examination was normal. On May 7 she developed a paralysis of her left limbs. Routine neurological examination showed a complete flaccid paralysis of the left upper extremity and a marked paresis of the left lower limb with slight movement at the hip and knee. A left homonymous visual field defect could be demonstrated grossly. The patient lay with her head and eyes deviated to the right. There was apparent astereognosis and loss of position sense in the fingers of the left hand. Vibratory sensation was less well perceived in the left limbs than on the right. Perception of touch and pin-prick was retained to single stimuli. Lumbar puncture yielded a clear fluid containing 25 crenated red blood cells and 4 white blood cells per c.mm. The total protein content was 20 mg.%. The EEG record showed a large amount of delta wave activity with frequencies as low as 1·2 cps. over the right side of the head.

The patient was interviewed daily until her death on May 31, 1952. She expressed explicit verbal denial of illness. She stated that there was nothing wrong with her left arm, and that she could move it but that it was not as "strong" as "quick" or as "swift" as her right. She claimed that she could walk but did not confabulate that she had walked. She complained of "loss of appetite," "a run down condition," a "kink" in her neck and worried if she were getting "rheumatism" or "polio." Throughout her illness she kept her eyes and head deviated to the right. However, she could turn her head and eyes to the left on command and pursuit. This posture persisted throughout her illness, even when her bed was placed in different positions and examinations carried out from both sides of the bed. She was incontinent of urine and fæces but did not deny their occurrence.

She was consistently disoriented for time of day, invariably giving an evening hour when interviewed in the morning, afternoon or evening. After May 22 she was disoriented for place, stating that she was in "an annex of *K* County Hospital, the Neurological Building" (patient had worked as a nurse in *K* County Hospital). She expressed temporal reduplication, stated that several of the nurses were also supervisors at *K* County Hospital. She expressed the idea that the attractive secretary who recorded the interviews was a "Miss Young" whom she had known previously, adding "they used to call me Miss Young because I looked like her." The patient showed nonaphasic misnaming (paraphasia) calling an emesis basin a "pen holder" and a roll of adhesive tape "an electric fixture," while naming correctly a group of objects not related to the hospital or illness.

The patient expressed the delusion that there was an "extra" or "false" hand lying across her abdomen while her own left arm lay at her side. She described the

"extra" limb as a hand and part of an arm. At times she said she had two left hands, on other occasions she said that the hand belonged to Mrs. D., a close friend and nurse who visited her daily. Twice she said it was the hand of a doctor. The patient described the hand as "heavier," "thicker," "bigger," "fatter," and "darker" than her own hand. She frequently referred to it as "hot and heavy" and "a woman's hand, hard working and well used." She said that there was nothing the matter with her own left hand. When the patient was asked to demonstrate the "extra hand" she would grope about her abdomen or in the space above it and say it was there or that she had pushed it away. If her own left hand was placed on her abdomen or raised in front of her she would identify it as the "extra" one. On one occasion she called it the "sheet," another time a "pyjama string." When the examiner placed his hand on her abdomen she named it correctly. When her left hand was shown to her in a mirror she pointed to the hand as one hand and to the wrist as another. There was no reduplication of any other part of the body. During the last week of her illness the delusion was less consistent with the left upper limb lying at the patient's side, but it could always be produced by placing the limb across the abdomen. During this period the denial of the hemiplegia was less marked, the patient saying, "the *doctors* think I had a stroke."

She usually seemed depressed and was apt to begin an interview by crying, complaining of pain and asking that her friend Mrs. D. take her home. However, when speaking of the "extra" hand she would become gay and bantering. If she were unable to "find" it she might remark "Oh, it will turn up after a while, just when you don't want it." When asked if the arm had changed at all she replied, "No, just as heavy; it's a nuisance—why don't you take it home with you. I'd like to know what your wife would say. You'd really have to make up a story." Once, in response to a query concerning her left hand, she said, "That's someone's hand, someone forgot it—that's funny, you read in the paper about people losing purses but not a hand—it's a very heavy one—maybe it's a foot." Although she often spoke of pushing it out of the way and went through the motion several times in interviews, such actions were not observed by the nurses when she was alone. At times she would remark how "ridiculous" it was for someone to have an idea that she had more than two hands, but would then reaffirm her delusion. When asked whether Mrs. D. had more than two hands, she replied, "That's a silly question, how could a person have more than two hands." Occasionally she was bitter about being sent to a "nut factory," i.e. the neurological ward, because of her hands.

On perceptual studies the phenomena of extinction, displacement and allesthesia could be demonstrated. She usually perceived single touch and pin-prick stimuli to the left side accurately. When double simultaneous stimuli were applied to the right and left sides she only felt the stimulus on the right. Simultaneous stimuli applied to the left hand and areas elsewhere on the left side as the cheek, neck or foot usually resulted in extinguishing the hand stimulus. Occasionally the hand stimulus was referred to the abdomen or to the "extra" hand. This would be demonstrated with the patient's eyes closed or open. When simultaneous stimuli were applied to the right side extinction could be demonstrated less frequently.

Occasionally a single stimulus to the left hand would be perceived on the right and if the left arm lying on the abdomen were stimulated the patient named her "false" arm. Allesthesia could be elicited by the use of a pin-prick stimulus to the left hand followed in a fraction of a second by a stimulus to the right side. Thus, when the left hand and the right hand were pricked in this fashion the patient frequently reported two pricks on the right hand. When stimulated in the reverse order the patient usually reported a single stimulus to the right hand. Allesthesia could be obtained only from the left hand and did not occur in the rest of the body and extremities. During the last week of the patient's life allesthesia could be elicited with single or alternating stimuli. When a stimulus was applied to the

left hand while it was placed on the right arm, she sometimes reported it on the right arm.

An account of their interpersonal relationship was obtained from the patient and her friend Mrs. D., the putative owner of the "extra" limb. Mrs. D. was a large, assured, white-haired person whose physical aspect contrasted with the patient's slight build. The patient compared them as follows—"She's big-boned. I'm thin and fine-boned. She's built like a truck horse, I'm built like a race horse. I was tall, built like a thoroughbred. In the dressing room one day I was getting ready to go on duty—she saw me and said, 'You're built like a thoroughbred.'" On one occasion when asked where Mrs. D. was the patient remarked, "out shovelling coal, I suppose." Mrs. D. described the patient as a person greatly concerned with pride and prestige which was manifested mainly in being "refined" and acting the "lady." She was secretive about her affairs and feelings, and the informant commented that she was supposed to take care of the patient but really knew very little about her finances despite a friendship of many years. The patient was very sensitive about her appearance, and the informant thought that she was considerably older than her stated age. She was extremely conscientious and punctual in her work and financial obligations. The informant considered her self-centred with few interests, little flexibility and initiative: the patient depended a great deal on her for guidance even in simple matters.

Autopsy Findings

General post-mortem disclosed carcinomatous metastases to the liver and kidneys with involvement of the lymph nodes. There was severe arteriosclerosis of the aorta and slight arteriosclerosis of the coronary arteries. Examination of the brain showed the cerebral hemispheres to be assymetrical. The right was swollen and softer. There was a herniation of the right cingulate gyrus beneath the falx for a distance of approximately 1 cm. The anterior cerebral arteries were pushed to the left by herniation of the gyri on the medial aspect of the right frontal lobe. On coronal section the entire right cerebrum was softened and friable. The left lateral and third ventricles were slightly dilated while the right lateral ventricle was obscured. Section of the brain-stem revealed numerous hæmorrhages in the mid-brain and dorsal portion of the pons. One of the hæmorrhages had ruptured through the floor of the fourth ventricle.

Case 2.—A 24-year-old soldier was admitted to the Walter Reed Army Medical Centre on May 11, 1952. On April 5, 1952, in Germany, he had been struck by an automobile and brought to a hospital in deep coma. A lumbar puncture yielded a bloody spinal fluid. Bilateral Babinski signs were elicited but an accurate neurological status was apparently difficult, because in addition to the disturbance of consciousness, there were fractures of the right fibula, tibia and metacarpal bones. A non-purulent effusion of the left knee-joint also developed. For the next three weeks he was noted to be lethargic, confused and incontinent of urine. Ventriculography showed dilatation of both lateral and third ventricles, and an EEG record taken on May 19 showed "abnormal slowing in the left frontal, right parietal and occipital leads." Another EEG record on June 3 showed slowing at the right frontal, temporal, parietal and occipital electrodes.

On admission to Walter Reed Hospital the patient was noted as "confused" and confabulating. He was grossly oriented for place and time, but misidentified the examiner and expressed the delusion that he had four legs. He was seen by the writers for the first time on June 6. He walked with a limp, favouring the left leg. Examination showed a slight left hemiparesis and a left Babinski sign. On the application of double simultaneous tactile stimuli, those applied to the left

side were usually extinguished or displaced to other parts on the left side. He described the feeling he had experienced that he had two pairs of legs, front and back. He indicated one pair in the usual position, and the other coming off at the hips. He said he had a feeling at other times that they had taken his legs away and he didn't know when they had been sewed back.

Although the delusion concerning his limbs had cleared, he showed many other reduplicative phenomena. He stated that he had also been paralysed after the First World War. He recalled having been in a Walter Reed Hospital located in New York at that time. He said that he had gone overseas with his father who had also joined the Army . (Father actually had never been in the Army.) He explained that he and his father had alternated being in charge of an operation, flying nurses between America and Europe. On his last trip back he said his mother had been on the plane as she had become a nurse. He claimed that his "first" paralysis had been caused by being scared on a plane and his mother had also been scared. There were also many instances of temporal reduplication of which the following are examples. He expressed the belief that the ward attendant was an old schoolmate of his. He said he had "recognized" the doctors who had taken care of him as friends from his home. The Chaplain in Germany likewise was a clergyman from his town.

He stated that he had not been paralysed when he entered the hospital in Germany, but only after he was put to bed. He expressed awareness of his limp and the fact of his operation. He had a scar on his leg as the result of a mole removed a year previously. He now stated that this had been made by a leash on which were fastened a dog and a cat which chased and fought each other. He remarked that several other patients also had had cats and dogs to amuse them in the same fashion. The patient's manner was bland and serene, and he expressed his delusions in a pleasant conversational tone with no evident agitation. He seemed undisturbed at being on a locked ward with psychotic patients. He jokingly remarked that he would tell his little sister that five girls had pulled his hair out. When asked to draw a picture of a person, he drew a figure with the back of the head left open. Most of the delusions persisted in repeated interviews during the next two weeks. He would talk of them in a stereotyped way, using the same phrases on each occasion. When a delusion was given up, he would refer to it as "my parents said 'he believed such and such.'" He no longer believed his parents had been in the Army. On June 19, the patient was given 0·4 gramme of amytal sodium intravenously. While under the influence of the drug he stated that he was talking to another patient who was lying next to him with his legs across his (the patient's) shoulders. He described the other man as being barefoot and wearing blue socks. (Patient was using his rolled up blue jacket as a pillow and the examiner was resting his hands at the head of the stretcher on which the patient was lying.) He also became disoriented for time and place, locating the hospital in Germany, then near his home, and stating there was another Walter Reed Hospital in Wheeling, West Virginia (reduplication for place).

During the next month the patient's condition improved. He said he had not actually been in two Walter Reed hospitals and no longer readily gave the names of the doctors whom he had "known" at home. He now recalled that he had a mole removed from his leg and expressed some doubt concerning the cat and dog story. He no longer believed he had been paralysed before. Extinction and displacement could no longer be demonstrated. On August 24 the amytal procedure was repeated. He showed no reduplicative phenomenon relating to body parts, time or place. However, he still insisted that the cat and dog tale was true even though "they still laugh at me."

Case 3.—A 29-year-old man was admitted to the Neurological Service of The Mount Sinai Hospital on June 20, 1952. There was a history of blurred and double

vision for six months, headache for three weeks and nausea and vomiting for one week. Neurological examination showed bilateral papilloedema, a slightly broad-based gait, increased deep reflexes in the left lower extremity and a left Babinski sign. The EEG record showed some high voltage sporadic 2–3 cps. activity over the posterior part of the head. On June 24 a sub-occipital craniotomy was carried out and a hard tumour invading the left cerebellar hemisphere and the floor of the fourth ventricle was subtotally removed. It was reported pathologically as an astrocytoma with anaplastic changes. Following the operation the patient developed a meningitis with a cerebrospinal fluid leak. The spinal fluid contained 1,000–2,000 white blood cells and the patient was treated with bacitracin intrathecally and penicillin systemically. On July 17 bilateral burr-holes were made and a catheter inserted into the right lateral ventricle for drainage. This was continued for a week with marked improvement and the spinal fluid leak cleared entirely ten days later.

On admission, the patient was completely oriented and had a joking bantering manner during interviews, referring to his illness as "morning sickness," but admitting his symptoms on further questioning. On June 24 he was interviewed after being given 0·3 gramme of amytal sodium intravenously. He became disoriented for place and time and denied being ill. He explained his situation by saying he was a prisoner of the Nazis who were trying to involve him in a plot. During the period of severe meningitis he became lethargic and restless. He was intermittently disoriented for place and time, but was aware that he had had an operation. "They put a hole in my head and drained out my brains." He was very bitter against the surgeon, particularly because he was made to sit up to facilitate drainage. He referred to the surgeon as a "hypomaniac" and "son of a bitch, he's trying to prove he's a better man. I give in." He confabulated that some nurses had tried to "shanghai" him aboard a ship, had held him "incommunicado." but that he had escaped.

On July 29, he expressed the delusion that he had three heads and four bodies. One head and body were with him, but the others were upstairs in a closet. The head with him had *not* been operated upon but was "empty." He described it "like a hunk of wood, having no use, no utility." He charged that "I'm being punished because my head drained wrong, so what." He attributed the bandage on his head to its having been hurt slightly in an automobile accident. He called one of the "other" heads his "main head" or "regular head" which had had pain but had been operated upon and now no longer had pain. He enumerated the "other" heads as "one willed to me, one a duplicate of the original, and one I grew for protection." The number of heads varied from four to six and there were three, four, or five bodies. The heads were the same size. He specified that the main head was "doing fine after the operation and had no bad drainage." "This head and body are sick, but the others are all right. They can go home." On July 30 he stated that he had six heads, "separate and distinct." He thought the one he had on was given to him several days previously, "it came in a box," so that when he got under his car he would not get greasy. He remarked that he could change heads "like a painter's cap." The patient appeared quite "clear" in that he spoke in a matter of fact tone and apart from his delusional content seemed quite rational.

In addition to reduplication of heads, the patient also expressed reduplication for place. He said that he was in the "water part" or "seaport" of the hospital, whereas previously he had been in the main part of the hospital on "solid ground." He located the "main part" correctly but stated that the water part was situated on the river (East River about $\frac{1}{2}$ mile away). It was in answer to a question concerning his orientation for place that the patient first mentioned the multiple heads. He also expressed delusions that some records were concealed in his pillow and that nurses had made sexual advances to him.

The head delusion lasted for four days. During this period he also showed "paraphasic" misnaming. He called a surgeon's rubber glove a "tobacco pouch" and then "a rubber glove to use in a garden." He named a doctor's bag as a "bag to carry junk." Adhesive tape was called "Scotch tape." However, objects not connected with surgical procedures were named correctly. Double simultaneous tactile stimulation of face and hand was perceived correctly, without extinction or displacement. When asked to draw his heads he made a series of circles.

After the delusion concerning his heads and bodies had cleared up, the patient said that he thought he had had six heads because his head had been bandaged six times. He thought there were multiple bodies because "each head has to have a body." His reduplication for the hospital persisted for several weeks longer. He remarked that he knew it was "logically impossible" but the feeling was too real to have been a dream. He also persisted for several weeks in believing that nurses had approached him for sexual relations. In his more disturbed phase he had commented on one occasion that this had consisted of a nurse handing him a bottle to fill. The patient was continent during the day but at night would be incontinent of urine and fæces. He associated this with very vivid dreams which he began to relate ten days after the disappearance of the head delusion. These were "colossal" in which "I'm master of the universe and everyone kowtows to me." The dreams were in technicolor and in them he had a circular office made of red oak. He recalled other dreams of great violence, shooting, etc.

The patient was discharged from the hospital on October 31, 1952. At home his wife reported him as being more childish and demanding but there was no recurrence of his delusions. On February 9, 1953, the patient was again interviewed with amytal sodium. After 0·5 gramme he manifested disorientation for year, intermittent disorientation for place and misidentification of the examiners. No reduplicative phenomena were found.

An account of the patient's premorbid personality was obtained from his wife. He was described as a very energetic, driving, competitive person whose main aims in life concerned making more money than other people and sexual achievement. He was conscientious, responsible and punctual in his business and wanted greatly to be a "success" and have the esteem of others. He tended to be dominating and to be critical and intolerant of others, particularly his wife. He seemed to have a great need to be superior. He was fastidious about his personal appearance. He was particularly self-conscious over a partial baldness. He desired greatly to be attractive to women and it was important for his prestige to make sexual conquests. He was said to have a good sense of humour and when anxious with people would joke. His health had been good, he never complained of physical ailments and didn't believe in medicines but felt that "sleep would cure everything."

Case 4.—A 51-year-old engineer was found in an unconscious condition on the stairs of a subway station on November 26, 1952. A bruise over the right side of his head and evidence of bleeding and flow of spinal fluid from both ears were noted. At the hospital where he was treated he was restless and irrational. Although it appeared to observers that the patient was blind he claimed that he could see and would describe turkeys walking about his room. He said his wife was always dressed in brown and thought he was in the Marines. He was transferred to a psychiatric hospital on February 27, 1953, and to the Mount Sinai Hospital one month later. Past history was significant in that in 1934 his left eye had been removed following an infection.

Examination on March 6, 1953, showed a right facial weakness of the peripheral type, deafness in the right ear, a right hemiparesis and right Babinski sign. The left eye was absent and there was a visual impairment in the right eye which could not be determined accurately. He was incontinent of urine. He was able to localize

single tactile stimuli fairly accurately but, when simultaneous double stimuli were applied, extinction and displacement on both sides of the body were noted. X-ray of the skull showed a large fracture extending over the occipital and parietal areas. The EEG record showed diffuse slow wave activity most marked in the left temporo-parietal region.

On being questioned concerning parts of the body he stated that he had four eyes, two heads, two bodies, four arms and four legs. He answered, however, that he was only one person. He indicated two eyes on one side of his head and two on the other. When asked what the difference was, if any, between the two bodies he replied, "Well, one of them is equipped with a head that operates—you might say—the other is equipped with a head that doesn't ordinarily operate." In addition to reduplication of parts of the body the patient showed reduplicative disorientation for place and time. He confabulated that he had seen the examiner before "around the laboratory." He named the hospital correctly but placed it in Philadelphia, remarking that he had been in the same hospital in New York (its true location) "once or twice." There was disorientation for date, the patient usually giving the year as 1952. There was a partial verbal denial of the hemiparesis. When asked if there was anything the matter with his right arm and leg he replied, "There is nothing the matter with them, but I'm not able to move them as well as I should." He said he could walk "sometimes" but did not do so often because of "laziness." The reduplicative delusion for parts of the body persisted for another three weeks; the patient claiming that he had three, four or five eyes and more than one head. On March 20 the patient said he had three eyes, two on the left and one on the right. He thought he could see better with the "left eyes." He denied having had any injury to his eye or an enucleation. In the interview of March 31, he admitted having only one eye but said that he had the "feeling" that he had more than one. During the next few weeks he expressed the feeling that he could see out of an unusually wide area with his right eye. When he was asked about the delusion he had had he often replied, "Well, you know the old expression, I saw it with my own too good eyes." A delusion that persisted was that the patient in the next bed, a Chinese, was a doctor who was giving spinal taps. He referred to the patient as a "Chinese iron-eyed bear."

On April 28 the patient was interviewed after being given 0·4 gramme of amytal sodium intravenously. Under the influence of the drug the delusions of multiple eyes and heads was again elicited. He said that he had two eyes with which he could see without trouble although admitting that he had lost an eye many years ago. He also stated that he had two heads, one of which "acted better" than the other.

The reduplication of the hospital continued throughout April and May. He named the hospital correctly but would call it the "suburban part" or the "convalescent part" or "branch" or "detachment" of the main hospital. He located the main hospital at its correct address but placed the "branch" in the suburb where he lived. He said that he had formerly been a patient in the "main hospital." There was intermittent temporal reduplication when the patient would confabulate that he had previously known or seen people whom he was actually meeting for the first time.

After the initial interviews the patient admitted his hemiparesis and inability to walk. These were at various times attributed to "a fractured arm," an "automobile accident in 1946" and to "being hit by a subway train." He confabulated that his eye had been lost in a recent accident.

In identifying objects the patient made many "paraphasic" naming errors. He called a syringe a "used radio-tube," a thermometer "a small aluminium tube—reminds me of a thermometer," a toy turtle "an electrical instrument of some kind," a roll of toilet tissue "a piece of paper out of some book-keeping machine," a rol of adhesive tape "a wooden ring of some kind," and coins "part of a safety razor.'

Psychomotor activity was retarded. He sat in his bed or chair for hours in an immobile fashion—as he once remarked, "like a potted plant." Though he responded promptly to questions he rarely made any spontaneous conversation. His speech was stereotyped and banal with many clichés. When asked how his arms felt he invariably replied "weak and sensitive." When repeatedly asked the question "If you had one wish what would it be?" the answer was "financial security." It was of interest that the patient never mentioned the reduplicative delusions about his eye or head to his wife.

An account of the patient's premorbid personality was obtained in interviews with his wife. He was described as a rather eccentric person with a great drive to improve himself. He had many interests which included Judo, longevity, body posture, diets, Buddhism, boating, guns and cameras. In both his work and hobbies he sought perfection, being a great reader of "How to ———" books. He was extremely self-conscious about his prosthesis and would always confront a person full face so that it would not be noticed. He was also concerned about his physical sexual potency. He had a great deal of stubborn pride, insisted on being "right" and getting his own way. He was secretive about his feelings, the informant remarking, "You could never get a straight answer from him." He tended to be saving about money but was extravagant on occasions in a "penny-wise pound-foolish" way. He had a habit of buying two of everything so that he would have an extra one if anything happened to the first.

Discussion

In the literature, the distinction between the delusional reduplication of parts of the body and cases in which there is an illusion of another member has not been made clearly. In these latter (Bechterev, 1904; Mayer-Gross, 1929; Lurje, 1936; Riddoch, 1941; Hasenjäger and Pötzl, 1941; Birkmayer, 1948; Hécaen, David and Talairach, 1945) the patient, as in the common phantom limb phenomenon following amputation, expresses awareness that he does not actually have an extra limb but it "feels" as if he had. Closely related to such experiences are illusions concerning the position of the limbs in space (Bechterev, 1894; Ostankov, 1904; Riddoch, 1917; and Lhermitte, Ducosté and Bineau, 1937). Van Bogaert (1934) described instances of illusional movements of phantom limbs and hemiplegic extremities. The importance of making such differentiations is obviously essential in any consideration of the relationship among anatomical, physiological, perceptual and conceptual factors. In this discussion we wish to point out our reasons for believing that delusional reduplication cannot be regarded either as (1) a specific defect resulting from the destruction of any particular area of the brain, (2) a manifestation of a perceptual disturbance caused by the interruption of a particular afferent system, or (3) a manifestation of an alteration in the "body scheme" in the sense that the body scheme is a three-dimensional image of the body with a representation in the parietal lobe.

From the standpoint of localization, illusional extremities may be associated with lesions of the peripheral nerves or spinal cord as well as the brain. Lurje (1936) reported the case of a 48-year-old man with a polyneuritis over a period of one week. The lower limbs were paralysed,

the upper paretic. The deep reflexes were absent in the lower limbs, sluggish in the upper. Speech was aphonic and regurgitation occurred. Deep sensibility was lost in all extremities and pain and thermal sensibility were diminished in "a pattern seen with peripheral nerve lesions." The patient declared a few days after admission, without being asked, that sometimes he felt as if he had three hands although he could not feel where any of his extremities were. He evaluated his sensations critically and ascribed them to his disease. Autopsy showed inflammatory changes in the peripheral nerves, none in the brain and spinal cord.

In the cases with delusional reduplication of body parts reported in the literature the pathology has involved the brain. In each of our cases the brain damage was extensive and of rapid onset. In two cases (2 and 4) there were severe head injuries with fractures of the vault and base in one instance and subarachnoid bleeding and subsequent dilatation of the ventricular system in the other. In Case 1 the entire right cerebral hemisphere was practically destroyed. In Case 3 a cerebellar astrocytoma infiltrating the floor of the fourth ventricle was associated with meningitis and increased intracranial pressure. Schenderov and Gamaleja (1935) made autopsy observations in 3 of their 6 cases. In one there was softening not only in the region supplied by the right middle cerebral artery but the frontal, parietal and occipital lobes as well. In the other 2 cases there were multiple foci of softening and diffuse arteriosclerosis. Meerovich's case of redoubling of the upper limbs was one of encephalitis. The only possible exception, in the literature, is the patient reported by Schaeffer (1942). She was 82 years old and had a flaccid quadriplegia as a result of a fracture of the cervical spine. She maintained that she had four feet and four hands. She had a temperature between 102·2 and 103·5° F. The patient died but no autopsy was obtained so that the extent of demonstrable brain involvement could not be ascertained. Brock and Merwarth's patient with the "parasitic" hand had clinical signs of widespread vascular disease including a probable basilar artery occlusion.

These studies indicate that the phenomenon, although occurring under conditions of altered brain function cannot be attributed directly to the destruction of any specific area such as the parietal lobe. These conditions appear to be provided by pathology of rapid onset with diffuse, multiple or deeply seated lesions which may or may not involve directly the parietal lobe. In each of our cases there was diffuse slow wave activity in the EEG record. In the case reported by Critchley (1952), for example, the right arm was paralysed because of the injury to the brachial plexus. The author assumes that the parietal lobe must have been damaged, yet the EEG showed "a good deal of abnormal slow activity, but symmetrical over the two hemispheres." The milieu of altered function may also be created by a combination of structural brain damage and the effects of drugs. In 2 patients reduplication could be elicited under the influence of intravenously administered amytal sodium after the delusion

was no longer manifested clinically. Schenderov and Gamaleja examined 2 of their patients with mescaline after the delusion had cleared. In one of the cases the reduplicative delusion returned, the patient saying he was unable to move his hand because an "extra heavy" hand was lying on top of it. While it is likely that there is involvement of the cortico-thalamic and reticulothalamic activating and inhibiting systems, many patients with these anatomical and physiological features do not manifest reduplication of parts of the body. It is evident that other factors must be considered.

Perceptual disturbances could be demonstrated in all four cases. In Cases 1 and 2 there was the usual kind of loss of gnostic sensibility that occurs with cerebral lesions. In Cases 1, 3 and 4 "paraphasic" naming errors were made. The term "paraphasia" is a poor one as it does not indicate the perceptual aspects of the phenomenon. The patient misnames an object in terms of a single aspect of its structure or function such as calling (Case 3) rubber gloves a "tobacco pouch." Jackson (1932) and Head (1926) referred to it as "imperception." In Cases 1, 2 and 4 alterations in perception could be demonstrated by the application of double stimuli arranged temporally or spatially. In Case 1 the phenomenon of allesthesia was elicited as the patient reported feeling pin prick stimuli applied in quick succession to the left (paralysed and reduplicated) hand, on the right. In Case 2, on double simultaneous tactile stimuli, those applied to the left side were frequently not perceived (extinction) or displaced. In Case 4, double simultaneous stimuli applied in many combinations evoked the phenomena of extinction and displacement. All of these perceptual phenomena may be observed in patients with brain disease who do not manifest reduplicative delusions. Although perceptual factors are obviously important, one cannot formulate an explanation of reduplication, as Bechterev attempted, solely in terms of any of our present concepts of perceptual function.

In considering the role of conceptual or symbolic factors, particularly those relating to the "body scheme," several facts are of significance. In each of our cases, and in those reported by others, the reduplicated member was one, which, in the patient's view, was incapacitated. While brain damage was present in all instances, the incapacity was not due necessarily to a lesion in the nervous system. In Case 2, the right leg could not be moved because of a fracture. In Case 4 the loss of vision resulted from an enucleation of the left eye performed many years previously. In Case 3, the patient said that his head did not function properly. Thus one cannot ascribe the reduplication of a part of the body to the effects of the lesion that causes the incapacity of that part as in hemiplegia. It cannot be stated that that lesion produces reduplication by destroying that part of the brain where "awareness" of the existence, shape, form or state of health of the limb is "represented." It appears rather that the lesion initiates a reorganisation of brain function, in which

any member that the patient conceives of as damaged may be reduplicated no matter what the cause of the incapacity. A similar point was ingeniously illustrated by Guthrie and Grossman (1952) who found that a patient who denied a left hemiplegia also denied her inability to move the right hand when it was tied down.

In addition to the reduplicative delusions concerning the body, each patient showed reduplication for place, time or person. Reduplication for place, the "reduplicative paramnesia" described by Pick (1903), may be defined as the confabulation of the existence of two or more places with almost similar attributes, although only one exists in reality. Reduplication for time is the confabulation that a present experience has been also experienced at some time in the past. Reduplication for person is the confabulation that there are two or more persons with similar characteristics although only one exists in reality. In a study of reduplicative phenomena reported previously (Weinstein, Kahn and Sugarman, 1952), it was found that reduplication was not limited to a single modality; spatial, temporal or personal. In each of the 4 cases under discussion, in addition to reduplication of parts of the body, there was reduplication in another sphere. In Case 3, for example, the patient not only doubled his lower limbs, but talked of another hospital of the same name, described another "paralysis" in the past, said his father was also a soldier in the Army engaged in the same work as he did and identified people on the ward with those he had known in the past. Shmarian (1934) noted that the patient who thought he had an extra hand also said that other patients were not only patients but old friends and relatives. It appears then that reduplication for parts of the body is but one manifestation of a more general pattern of reduplication, using the body as the particular element or modality of expression. For this reason it is better to refer to the phenomenon as reduplication rather than the more limited "pseudomelia."

In the earlier study it was pointed out that the "extra" place, person or time often differed from the original in some respect that provided a satisfaction of a wish or a need. This related particularly to the patient's problems concerning his illness. Thus the "extra" hospital might have the same name and the same personnel as the original but differs in that "operations are not performed" and "only convalescent patients are treated." A woman who had been operated upon for a metastatic brain tumour said she had twin sons Bill and "Willie" although actually she had one son referred to as Bill. She described the real son as he was, ascribed the same appearance and history to "Willie" but confabulated that "Willie" had been ill and was convalescing. One of her personal disappointments had been that Bill had changed his surname. However, she remarked that "Willie" had not changed his name. Similarly, the reduplicated part of the body is described as different in some way. Most commonly the distinction is made between the "good" and "bad" arm or head or whatever part of the body is involved. Otherwise the re-

duplicated part varies in terms of temperature, "warm" or "cold," or in size, "larger" or "smaller," in weight "heavier" and "lighter," or is regarded as "strange" or "foreign" in some way. Sometimes the part involved is projected outside of the patient's own body. Nielsen (1938) described a patient with a right hemiplegia who said that someone else's arm was in bed with her and her own right arm was on the floor. In Case 1 the patient said the extra hand belonged to her friend. In Brock and Merwarth's patient the hand was his daughter's.

The extra member of the body may likewise be used as a means of expressing some motivation or feeling. Thus the patient's description, in Case 3, of the "main head" as "doing well," having "no bad drainage," and not having pain appears to be a symbolic representation of his wish to deny the reality of his illness. His statement about the "water part" and "solid part" of the hospital probably refers to the problem of drainage from the operation wound which had disturbed him. In Case 1, the "thicker," "bigger" paralysed hand "belonged" to the friend while her own hand was said to be intact by the patient. This displacement of the paralysed limb to the friend appeared to symbolize certain aspects of the relationship between them. In Case 4 the feelings about his blindness are expressed in a number of symbol patterns: the confabulation that he could see, the reduplication of eyes, the denial of the enucleation and the peculiar delusion about the "iron-eyed bear."

The relationship among the brain pathology, the level of symbolic expression and the role of motivation appears to be similar to that found in other forms of anosognosia (Weinstein and Kahn, 1950), in disorientation for place and time (Weinstein and Kahn, 1951) and in "paraphasia." These phenomena are constantly recurring patterns which appear under similar conditions of brain function. The elements of these patterns are determined largely by the patient's motivation and particular life experience. Thus denial or unawareness of a defect as a paralysis, attributing the incapacity to some trivial complaint, projection of the incapacity to another person or into extra-personal space and displacement of an incapacity into a time in the past commonly appear in the same patient and appear to be variants of a single phenomenon. They are not unitary defects due to the destruction of any particular area of the parietal lobe or its connexions, nor do they represent discrete physiological processes or individual perceptual mechanisms. They are rather symbolic expressions of the drive to be well. The lesion produces a milieu of brain function in which the patient's denial of whatever he feels is a problem may be maintained. Thus one does not find reduplication or any other form of denial of a healthy limb. The role of motivation is also apparent in the "paraphasic" misnaming where the patient makes errors with objects related to illness while others of equal complexity and familiarity are named correctly (Weinstein and Kahn, 1952). Paterson and Zangwill (1944) similarly described the importance of the patient's drive to be

well and leave the hospital in determining the elements of the patterns of disorientation for place.

The fact that reduplication occurred not only with parts of the body but temporally and spatially as well, the association with damaged members of the body, and the lack of evidence of a focal lesion of the parietal lobe makes it difficult to explain the phenomenon as a disturbance of body scheme in the usual sense of a three-dimensional image of the body. This concept, moreover, does not consider the role of the motivation of the wish to be well. In reduplication, the "extra" part of the body, like the "extra" hospital, is a symbolic expression of the patient's feelings about his defect. Unless one uses the idea of "body scheme" as a concept involving not only the body itself but environmental, interpersonal and temporal factors the idea is not useful in interpreting the mechanism of reduplication.

An interesting point is the speculation as to what degree the phenomenon is what Rioch (1952) has termed "an artifact due to a particular type of communication occurring in dyadic groups." For example, the patient in Case 1 would repeatedly brush away the "false hand" during interviews. She never did this, however, outside of the interview situation. In a sense, the delusion existed only when the patient was confronted by the examiner. At other times she did not act in a way to distinguish her from other patients on the ward. Some patients with anosognosia may admit paralysis or some other defect to relatives and not to doctors. It may be that the stress of the interpersonal situation of the examination calls these symbolic defences into being. These remarks may be relevant to the behaviour of patients who, though expressing bizarre delusions and denying illness, yet submit to hospitalization and accept treatment without demurral.

It has been pointed out that many of the symbolic mechanisms described occur in normal persons under certain conditions. Thus denial, reduplication and disorientation are common in dreams. Temporal reduplication occurs as the familiar *déjà vu* experience. Paraphasic language is common in slang, prayer and nicknames. In myth, folklore and art, reduplication of parts of the body are themes that express the feelings and motivations of a culture. In Oriental art particularly, gods are portrayed with many heads to indicate great wisdom and many arms to express great strength or many skills. In our patients are reminiscences of the hundred-armed giants Briareus and Gyes, the Hydra where the loss of one head was replaced by two others, the four-legged Centaurs of Mt. Pelion and Argus the many-eyed watchman. What appear as bizarre curiosities are actually meaningful patterns of behaviour related to other manifestations of symbolic expression.

Summary

Four cases are described in which there were reduplicative delusions of the existence of extra parts of the body. One patient with a left

hemiplegia confabulated having an extra left hand; another with a left hemiparesis and a fracture of the right leg stated that he had four legs; a man with a cerebellar astrocytoma and meningitis confabulated having multiple heads and a patient with a severe head injury who previously had an eye enucleated expressed the delusion that he had several eyes. In all cases the pathology was of rapid onset and associated with a diffusely slow-wave EEG record.

In each case reduplication of body parts was associated with other forms of reduplication for time, place or person. Accordingly, the phenomenon is considered as being but one manifestation of a general pattern of reduplicative delusions.

Reasons are given why such delusions cannot be explained either as a specific defect resulting from the destruction of any particular area of the brain, as a perceptual disturbance, or in terms of an alteration in "body scheme" in the sense that the body scheme is a three-dimensional image of the body with a representation in the parietal lobe.

The delusion of reduplication occurs under the same conditions of altered brain function as do anosognosia, disorientation for place and time, and "paraphasia." As with these phenomena, the patterns of reduplication may be used as symbolic mechanisms to express some personal motivation, particularly the denial of illness.

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CRANIAL AND INTRACRANIAL MYELOMAS

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Involvement of the nervous system is one of the commonest complications of multiple myelomatosis. The incidence of brain and orbital manifestations is, however, difficult to discover because authors have not given separate figures for the various parts of the nervous system. They are rarer than spinal cord compression due to myeloma and their infrequency is demonstrated by the fact that in a series of 83 cases of this disease (Bayrd and Heck, 1947) none had direct brain or orbital involvement. An impression of their rarity in neurological practice may be gained from Cushing (1932) who found that among 2,000 intracranial tumours, there were only 4 cranial myelomas.

In the absence of any previous survey of the subject, this paper reviews the various neurological features that have been observed in cases with cranial and intracranial myelomas and, in addition, orbital myelomas are considered. A classification of clinical syndromes is suggested and 4 illustrative cases are presented. A patient may show evidence of intracranial or orbital encroachment at any stage of the disease. In occasional patients, however, this may be the first manifestation and they are seen initially by those dealing with neurological or ophthalmological disorders. The cases described here are of this type.

Classification of Cases

Cases with cranial or intracranial myelomas can be broadly classified into three clinical groups.

Group I: Syndromes of cranial nerve palsies.—These cases have one or more lesions in the base of the skull producing single or multiple cranial nerve palsies.

Group II: Intracranial tumour syndromes.—The clinical picture is like that of a brain tumour, and cases can be further subdivided into those in which a cranial myeloma extends intracranially and those where the lesion is entirely intracranial. Thus there may or may not be involvement of the skull bones.

Group III: Intra-orbital tumour syndromes.—The orbit may be invaded, and the clinical picture of an orbital space-occupying lesion produced.

Group I: Syndromes of Cranial Nerve Palsies

By 1928, there were 425 cases of multiple myeloma in the literature (Geschickter and Copeland, 1928) but in only 9 of the reports are cranial nerve palsies mentioned Altogether there are now 30 published cases of this type, but those of Senator (1899), Venturi (1901), Meyerding (1925), Canestro (1927), Heilmann (1928) and Snapper (1949) must be excluded because of insufficient clinical or pathological details; those of Neumann (1929) and Bruch (1934) were probably not examples of myelomatosis. There are thus 24 adequately described and histologically verified cases of multiple myelomatosis with cranial nerve palsies and to these another is added.

Case 1.—*Female, 61 years. Four-year history of diplopia, right visual impairment and bilateral deafness. One year of nasal obstruction and tingling right face. Involvement of right second, fifth, sixth and eighth cranial nerves and left eighth. Nasopharyngeal mass shown by biopsy to be a plasma cell myeloma. Extensive destruction of skull base with evidence elsewhere of multiple myeloma. Treatment with deep X-rays and urethane. Survival six years after first symptom.*

Mrs. E. E. W. (N.H. No. 32835), a housewife aged 61, was admitted to the National Hospital, Queen Square, on August 9, 1951, under the care of Sir Charles Symonds. Her family and past histories were not relevant. Four years previously, she had rapidly become deaf in the right ear and, at the same time, experienced a brief episode of diplopia which recurred intermittently over the next two years. One year before admission, the vision in the right eye gradually began to fail and, when she reached hospital, she could only distinguish shadowy outlines with it. For one year, the hearing in the left ear had been affected, but less severely than on the right side. There was loud tinnitus bilaterally. Bilateral anosmia had been present for one year, and she had recently noticed a tingling sensation on the left side of the face. At no time had she suffered any pain.

Examination.—Her general condition was good, but she was so deaf that contact could only be made by writing. The nasal septum was deviated to the left and in the right posterior nares there was a soft, purplish, polypoid mass that seemed to be growing from the roof of the nasopharynx. She was unable to smell any of the test odours, but there was complete nasal obstruction. Visual acuity in the right eye was reduced to hand movements in the upper nasal field only, but vision on the left was J.14, with correction. The right optic disc was paler than the left, and there was a bitemporal hemianopic type of defect with much more impairment on the right than on the left. The right pupil reacted poorly to direct light but briskly to consensual stimulation, and there was a partial right sixth nerve palsy. The right trigeminal nerve was intact and there was no facial weakness. Severe bilateral deafness of mixed type, more marked in the right ear, as well as complete right vestibular paralysis, could be demonstrated. The rest of the central nervous system and the other systems were normal.

Investigations.—X-rays of the skull (fig. 5) showed an extraordinary degree of destruction of the bones of the skull base. Anteriorly, this involved the sphenoidal sinus and the posterior walls of the antra, and laterally the apices of the petrous temporal bones were destroyed completely. There was a soft tissue shadow within

the nasopharynx. *Chest X-ray* was normal. *Cerebrospinal fluid* (C.S.F.): Pressure 100 mm., 3 cells, 50 mg. per cent protein, Lange 0001110000, Wassermann reaction (W.R.) negative. *Left percutaneous carotid angiogram:* The carotid siphon was elevated and in the lateral views the soft tissue shadow previously noted contained many pathological vessels and the internal maxillary artery was unusually large. *Biopsy* (August 29, 1951): Mr. C. P. Wilson at the Middlesex Hospital made a biopsy of the nasopharyngeal neoplasm, and microscopic examination revealed a typical plasma cell myeloma (fig. 1).

Additional investigations.—Blood: Hæmoglobin 79 per cent, red cells 4·1 million, white cells 12,600 (differential count normal), erythrocyte sedimentation rate (E.S.R.) 62 mm. in the first hour (Westergren), W.R. negative. *Serum proteins:* Total protein 9·3 grammes per 100 ml., albumin 2·7 grammes per 100 ml., globulin 6·3 grammes per 100 ml., fibrinogen 0·34 grammes per 100 ml. *Bone-marrow examination* (sternum) showed a slight increase in plasma cells but no conclusive evidence of myelomatosis. *Urine:* No Bence Jones proteinuria was found on repeated testing. *Further X-rays* revealed myelomas of femoral shafts, humeri and radii, as well as doubtful areas of erosion in the right second and left ninth ribs.

Progress.—She was given deep X-ray irradiation (total dose 4,900 r) directed to the base of the skull, and a course of 78 grammes of urethane. When discharged home on November 8, 1951, there had been improvement in her nasal airway, and the right sixth nerve weakness was less marked. She was last seen in August 1953, two years after discharge, and was continuing to improve. Her general condition was excellent, diplopia had disappeared and vision particularly in the left eye was much better; there was a dense central scotoma on the right. She could now hear a shouted voice and the sense of smell was normal. New bone was forming at the base of the skull, but the long bone myelomas were still present. The nasopharyngeal mass persisted. Apart from a slightly increased total serum protein, the blood was entirely normal and no Bence Jones proteinæmia could be detected.

Comment.—The cranial lesion in this case was thought to be a nasopharyngeal carcinoma and the mixed type of deafness was compatible with this conclusion; other possibilities were a chordoma or a metastatic deposit. After biopsy, further investigations revealed ample evidence of a much more widespread disease, despite the fact that all the symptoms and signs were referable to the skull lesion which thus might have been termed "solitary". This case, therefore, illustrates the type of process usually known as a "solitary" myeloma or "plasmacytoma." If adequate investigations (X-rays of long bones and ribs, E.S.R., serum proteins, urinalysis for Bence Jones proteinuria and bone-marrow biopsy) and follow-up are instituted, however, they can, almost always, be shown to be variants of myelomatosis. If evidence of the generalized disease is not found, it will develop months or years later. The patient here has survived six years and is thus an example of the type in which the usual bone pains and fractures, short history and general debilitation are absent and progression is very slow. The erosion of the skull base was a very striking feature and is comparable in extent with that present in the case reported by Wright (1953), where clinical data, however, are inadequate.

Pathology

Of the 25 cases constituting this group (Table I), 15 had evidence of the generalized disease and the others were either presented as examples of the "solitary" type, or data was insufficient. It is doubtful, however, if these were truly "solitary," as all the necessary criteria had not been satisfied.

The lesion of the skull base.—The base of the skull, as well as the vault, may be involved in myelomatosis and there is a grouping of the lesions around the sella turcica. The body of the sphenoid and the apex of the petrous bone are the commonest sites and the tumours may be either small and discrete or grow to large dimensions. The bone is probably their tissue of origin, but it has been suggested by Cappell and Mathers (1935) that they may arise from mucosa contained within the sphenoid and petrous bones, for non-osseous myelomas are not uncommon. The nasopharyngeal mucous membrane has also been incriminated but it has been satisfactorily shown by Stout and Kenney (1949) and Wright (1953) that any involvement of this tissue—as for example occurred in Case 1—is secondary to a bony tumour. Although the calvarial dura mater may be the seat of myelomas, there is no evidence to suggest that a similar event occurs in the basal portion of this membrane other than the tentorium cerebelli (Group II).

Cases have been described where the basal myeloma has invaded the orbit on one side, further jeopardizing the function of the ocular motor nerves (Seeman, 1930; Piney and Riach, 1931, Case 1; and Christophe and Divry, 1940, Case 1, among others).

The dural covering of the basal myeloma is usually intact and the cranial nerves are affected either by local distortion, or direct destruction as occurs, for example, when the tumour invades the cavernous sinus or jugular foramen region. Invasion of the nerves as may occur in other malignant lymphadenomas (Sparling, Adams and Parker, 1947) has not been observed in these cases. Langdon (1939) suggested that the neural dysfunction might be due to "toxins," and therefore akin to the polyneuritis that very occasionally accompanies myelomatosis. There is, however, no proof of this.

Legends for Figs. 1—4 opposite (*page 65*)

FIG. 1 (*Case* 1).—Myeloma of the base of the skull formed mainly of well-differentiated plasma cells. (× 500.)

FIG. 2 (*Case* 2).—Myeloma of the left side of the cranium. Most of the cells are typical plasma cells. (× 580.)

FIG. 3 (*Case* 3).—Myeloma of the tentorium cerebelli consisting mainly of plasma cells, but a few undifferentiated round cells are also present. (× 500.)

FIG. 4 (*Case* 4).—Myeloma of left frontal bone and orbit in which the elements are chiefly of the plasma cell type. (× 580.)

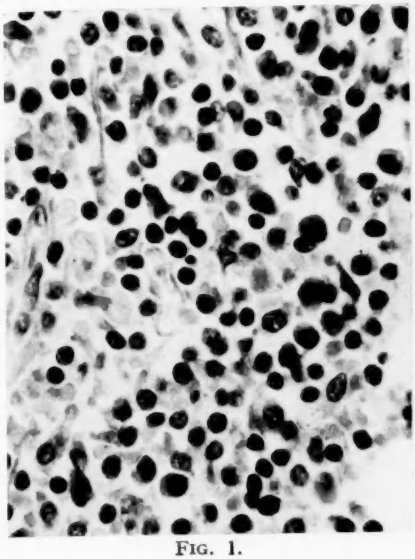

FIG. 1.

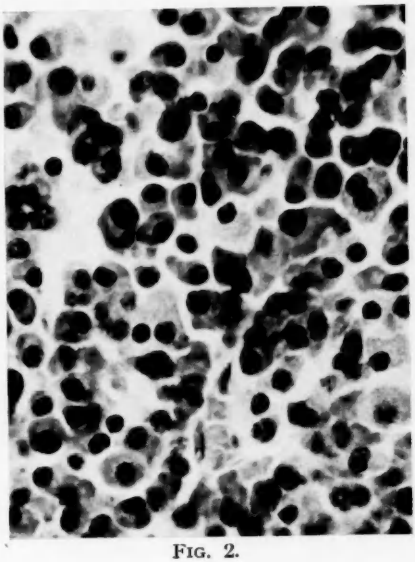

FIG. 2.

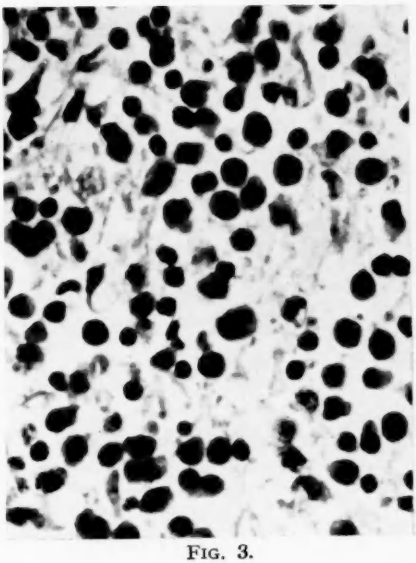

FIG. 3.

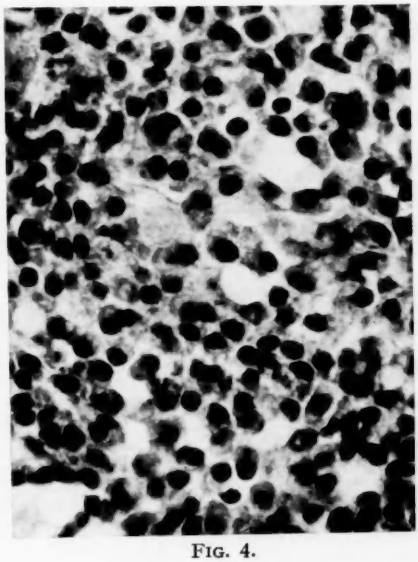

FIG. 4.

FIG. 5.

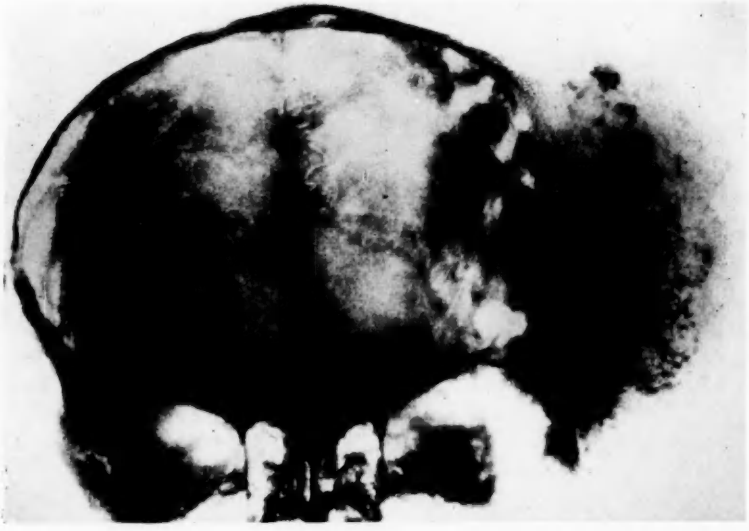

FIG. 6.

Clinical Features

The 25 proven cases of myeloma of the skull with cranial nerve palsies are reported in enough detail to make intimate consideration possible (Table I).

Age and sex.—These are comparable with the findings of Geschickter and Copeland (1928) and others who studied large series. The age of the patient at the onset of the illness could be estimated in 22 cases in this series and the range was 33 to 69 years, with an average of 51. (The 16-year-old patient of Calvet, Gayral, Claux, Rascol and Cadenat (1950) has been excluded because of the unusual age of onset of the disease.) There were twice as many males as females.

Initial features.—The first manifestation of the disease may be due to the cranial lesion and this occurred in 14 of the 25 cases. Thus 5 began with headache, 3 with ocular symptoms (diplopia or visual impairment), 2 with deafness, 2 with a facial nerve palsy, 1 with trigeminal nerve palsy, and 1 with amenorrhœa and polydipsia thought to be due to hypothalamic or pituitary involvement. Otherwise the neurological features develop during the course of the generalized disease as occurred in the remaining 11 cases.

Cranial nerves involved.—The sixth nerve is most frequently affected (15 among 25 cases) and occasionally this may be bilateral. Next in frequency is the eighth nerve with varying degrees of unilateral or bilateral deafness which is often of the mixed type, thereby simulating the naso-pharyngeal carcinoma or similar invasive lesion. Thirdly, there is the trigeminal nerve, the peripheral divisions of which may be encroached upon as well as the intracranial portions. The remainder of the nerves are involved less commonly. At times, only one nerve is affected (commonly the sixth), but, on the other hand, various syndromes of multiple cranial nerve palsies occur.

Investigations.—Cerebrospinal fluid: There is very little data dealing with the C.S.F., for in only 10 of the 30 case-records is it mentioned. Of the 6 abnormal fluids a slightly increased pressure or protein and a mild lymphocytic pleocytosis were the usual findings. The dura is an effective barrier to the myelomas for only Khondkarian (1951) mentions plasma cells in the C.S.F. The Lange reaction may on occasions show a very strong paretic curve although the W.R. is invariably negative (Moeschlin, 1943). This is presumably due to an excess of globulin which has been shown by electrophoresis to be present in the C.S.F. as well as in the serum (Labhart, Schweizer and Staub, 1951). *X-rays of the skull* may reveal osteolytic areas in the vault as well as in the base.

Legends for Figs. 5—6 opposite (page 66)

FIG. 5 (*Case* 1).—Radiograph to show the base of the skull and the extensive bony erosion produced by the myeloma.

FIG. 6 (*Case* 2).—Radiograph of the skull showing the massive cranial myeloma containing flecks of calcification. Large vascular channels are seen in the skull vault.

TABLE I

GROUP I.—PUBLISHED CASES OF MYELOMAS WITH CRANIAL NERVE PALSIES

Case No.	*Author and date*	*Sex*	*Age*	*Initial features of illness*	*Duration of cranial nerve palsies*	*Total duration of illness*	*Cranial nerves involved*	*Principal lesion of skull base*	*Multiple or single*	*Outcome*
1	Stokvis (Kühne, 1883)	M	40	Loss of weight and back pain	1 week	9 months	5, 7	Basal myeloma? (Kahler, 1889)	M	Death (no P.M.)
2	Hammer (1894)	M	47	Joint and back pain	6 months	13 months	6	Middle fossa	M	Death
3	Ritter (1921)	M	37	Pain in limbs Back pain	2 years 9 months+	2 years 10 months+	6	?	M	?
4	Pallestrini (1927)	M	45	Mass in nasal cavity	?	?	2, 5	?	?	Death (no P.M.)
5	Riser and Sorel (1929)	M	61	Headache and facial palsy next day	13 months	13 months	4, 5, 6, 7, 8, 9, 10, 11, 12	Sella Clivus (X-ray)	M	Death
6	Sabrazès *et al.* (1931)	M	71	Rheumatic pains and fractures	5 months	8½ years	6, 7, 8	Petrous bone	M	Death (no P.M.)
7	Cabot (1934)	M	39	Trigeminal palsy	14 months	14 months+	3, 4, 5, 6, 7, 8 (R) 6 (L)	Sphenoid bone Petrous bones	M	Death
8	Pollock (1934) Case 2	M	39	Facial palsy	14 months	14 months	7+	Sphenoid bone Cavernous sinus	M	Death
9	Cappell and Mathers (1935)	F	57	Facial palsy	4 years	4 years	6, 7, 8, 9, 10, 11	Sphenoid bone Petrous bone	?	Death
10	Fowler (1938)	M	61	Loss of weight	?	About 8 months	8	Petrous bone	M	Death
11	Langdon (1939)	F	41	Headache	14 months	16 months	1, 6 (R) 1, 2, 6 (L)	Sella (X-ray)	M	Death
12	Christophe and Divry (1940) Case 1	F	56	Headache	*c.* 9 weeks	3–4 months	1, 2, 3, 4, 5, 6	Sphenoid bone and orbital fissure	M	Death

13	Christophe and Divry (1940) Case 2	F	42	Amenorrhœa Polydipsia	3 years+	9 years	1, 2 (R) 1, 2, (L)	Sphenoid bone Petrous apices	?S	Death
14	Godtfredsen (1944)	M	52	Nasal	? 4 months	8 months	6	?	?S	Death from intercurrent disease
15	Gros (1945)	F	67	Deafness	4 years	4 years	5, 6, 8	Petrous apex	?S	Alive
16	Figi, Broders and Havens (1945) Case 6	F	47	Nasal obstruction and deafness	2¾ years	2¾ years	2, 8	Sella	?S	Alive
17	Walsh (1947)	—	—	Sudden blindness	?	?	1, 2, 8	Sella Petrous apices (X-ray)	?	?
18	Sparling *et al.* (1947) Case 20	M	70	Headache	6 months	11 months	5, 6, 7, 8, 9, 10, 11, 12	Sella Petrous bones	?S	Death
19	Sparling *et al.* (1947) Case 21	M	66	Weakness and weight loss	?	1 year 11 months	6 (R) 2 (L)	Sphenoid bone	M	Death
20	Smith and Gault (1948)	M	56	Headache	?	6 months	2, 6	Sella Middle fossa	M	Death
21	Calvet *et al.* (1950)	M	16	Apathy and fatigue	4 months	6 months	3, 4, 5, 6, 7, 8, 9, 10, 11, 12	?	?S	Death (no P.M.)
22	Lane (1950)	F	46	Pain in left knee	1 month	14 months	10, 12	?	M	Death (no P.M.)
23	Cagnoli and García Novales (1950) Case 3	M	42	Pathological fracture right ulnar	3 months	7 years	3	Sella (X-ray)	M	Alive
24	Delmas-Marsalet *et al.* (1951)	M	64	Diplopia	1¼ years	1¼ years	3 (R) 3, 4, 5 (L)	Sella Left petrous apex	M	?
25	Case One	F	61	Diplopia	6 years	6 years	2, 5, 6, 8 (R) 8 (L)	Sella Petrous apices	M	Alive

Urinalysis: As in other cases of myelomatosis, the frequency with which Bence Jones proteinuria occurs is determined by the frequency of observations. It was looked for in 7 of these cases and found in only 3. *Bone-marrow biopsy* may be of great diagnostic value but it was employed only three times in this series and was of diagnostic value in only one.

Diagnosis.—The plasma cell myeloma must be considered when dealing with lesions that erode the skull base, such as a nasopharyngeal carcinoma, extra-sellar extension of a chromophobe adenoma, chordoma or primary, malignant neoplasm of the sphenoid or petrous bones. An eosinophilic granuloma may produce a similar picture. The diagnosis of this type of cranial myeloma rests finally upon biopsy examination and upon the search for other evidence of myelomatous disease.

Prognosis.—The average length of the whole disease in this group was about two years, which corresponds closely with the survival rates usually quoted for myelomatosis. The range in the series surveyed was from six months to nine years, although the latter patient (Christophe and Divry, 1940, Case 2) died soon after operation. The cranial nerve palsies may be present for one week or six years and in only 2 cases (Hammer, 1894; Sparling *et al.*, 1947, Case 21) has remission without treatment been observed. As is to be expected, the cases with multiple spread ran a shorter course than those with "solitary" myelomas, although Case 1 is a striking exception. On the other hand, although it appears that they survived longer it is difficult to evaluate the so-called "solitary" myelomas reported in the literature for it cannot be certain that other evidence of the disease was not, in fact, present. Except perhaps for those patients with bulbar palsies, death is invariably due to the generalized disease and not to the cerebral involvement.

Group II.—Intracranial Tumour Syndromes

A myeloma of the skull may extend into the cranial cavity or a myeloma may grow from intracranial structures to produce features of a space-occupying lesion. Cases can therefore be divided into those with and those without a skull lesion.

(*A*) *Cases with Myeloma of the Skull*

Pathology.—Despite the fact that the calvarium is one of the commonest sites for myelomas, cerebral involvement is rare; no accurate assessment of its incidence is, however, available. The lesions may be single and large (Courville, 1948) or multiple and small, or a combination of these two varieties is found. On rare occasions the tumour grows through the dura mater but invasion of brain tissue never results and cerebral dysfunction is produced by direct pressure only.

The dura mater is the only non-osseous, intracranial structure that

can produce a plasma-cell myeloma and involvement may be of two types: (1) *discrete myelomas*, which are much more common than Armstrong, Faulds and Stewart (1946) suggest, and (2) *diffuse infiltration* such as was found in the cases of Piney and Riach (1931, Case 2), Davison and Balser (1937, Case 5) and Sparling *et al.* (1947, Case 18) and may also occur in the spinal dura.

Clinical features.—Cranial myelomas of these types may produce a variety of neurological manifestations, the resultant clinical picture being dependent upon the location and the degree of intracranial extension. The visible portion of the tumour, however, is not necessarily a guide to the latter. Discrete myelomas of the convexity dura behave exactly as do their bony counterparts and, as they produce erosion of the overlying bone, they are included here. Infiltration of the dura mater, however, is symptomless and does not behave like carcinomatosis of this membrane. It has been claimed by Laurentius (1938) that it may induce meningeal irritation but there is no reliable evidence for this.

Increased intracranial pressure.—This has been described in 7 cases of myelomatosis, by Meyer (1913), Meyerding (1925, Case 2), Kalischer (1928, Case 1), Wilson and Milkman (1932), Balan and Ballif (1932), Krainin, D'Angio and Smelin (1949) and James and Turner (1952). The usual clinical features of intracranial hypertension are present, often associated with focal neurological abnormalities, and death is in some cases due to this state. Multiple tumours were found in all these cases, but in half of them, one myeloma was considerably larger than its fellows.

Focal features.—Like the preceding, these are rare and comprise contralateral facial and limb weakness (Kalischer, 1928, Case 1; Villata, 1928; Balan and Ballif, 1932; Khondkarian, 1951) or only reflex changes (Cabot, 1934). Cerebral compression by either a calvarial or dural myeloma produces these signs. Hemianopia has been described only once (James and Turner, 1952).

The following case may be added.

Case 2[1].—*Male, 53 years. Lump on left side of head for four years gradually increasing in size. Weak left arm and leg, headaches and giddiness for two months. Left-sided cranial tumour 17 × 8 cm. with minimal left hemiparesis. Partial removal of myeloma and treatment with radiation. Tests for multiple myeloma not done. Death after fits, aphasia and paralyses had appeared. Six years' survival. No autopsy.*

H. H., a cafe proprietor, of 53, was admitted to the Radcliffe Infirmary on February 18, 1944, under the care of the late Sir Hugh Cairns. His past and family history yielded no relevant information. He was right handed. For four years he had noted a pulsating, painless lump in the left parietal region which had gradually increased in size, but more rapidly over the preceding four to five months. He also complained of postural vertigo, occasional headaches, and for two months the left limbs had become progressively weaker.

[1]Case 2 and Case 4 have been mentioned already by Northfield and Russell (1951).

Examination.—There was a large, bilobular tumour of the skull mainly fronto-parietal in location, measuring 17 cm. in diameter and protruding 8 cm. from the skull surface. Apart from slight weakness of the left lower face, arm and leg, and an equivocal plantar response on that side, the central nervous system was normal.

Investigations.—*X-rays of the skull* revealed that almost the whole of the left side of the cranium had been eroded by the tumour and there were huge vascular. channels leading to it. In the tumour there were many flecks of calcification (fig. 6). *C.S.F.:* Pressure 265 mm., 2 lymphocytes, 15–20 mg. per cent protein, Lange no change, W.R. negative. *Blood:* Hæmoglobin 70 per cent, red cells 3·9 million, white cells 18,000 (differential count normal).

Operation, February 24, 1944 (Mr. J. B. Pennybacker).—An attempt was made to excise the tumour but the patient's condition throughout the operation was very precarious and only a small portion of it could be removed. The dura was seen only in the occipital region and it appeared normal.

Histology.—Dr. A. H. T. Robb-Smith reported that the neoplasm was a plasmacytoma. Typical plasma cells were lying in sheets without any pattern (fig. 2). A material thought to be amyloid was also seen.

Progress.—His post-operative recovery was uneventful and he was given a course (5,000 r) of radiation therapy and another one year later. Two years after the operation he was not having headache and there was no evidence of increased intracranial pressure. The postural vertigo was still present, and the left-sided signs were unchanged. Three months later, however, he had transient attacks of aphasia and on December 23, 1946, he died, six years after he first noted the skull tumour. Before his death he had suffered from epileptiform seizures and limb paralyses. Unfortunately, additional information could not be obtained and an autopsy was not carried out.

Comment.—The clinical picture, and probably death, were due in this case to the cranial myeloma but it cannot be termed "solitary" as a search for evidence of myelomatosis was not made, nor was an autopsy performed. The tumour was, however, slow-growing and perhaps held in check by radiation therapy. The ipsilateral signs may have been produced by tentorial pressure on the displaced cerebral peduncles, but terminally there was evidence of direct cerebral involvement. Increased intracranial pressure may have been present terminally but it was otherwise absent; the one raised C.S.F. pressure reading is of doubtful significance. The calcification within the tumour is an unusual feature but has been described by Krainin *et al.* (1949). The association of myeloma with primary amyloidosis is well recognized.

Epileptiform manifestations.—These are no doubt due to cortical irritation by the compressing tumour and various types have been described by Dick (1904), Kalischer (1928), Ellermann and Schrøder (1933), Pollock (1934, Case 2), Denker and Brock (1934, Case 1), and Christophe and Divry (1940, Case 2) as well as Case 2 where fits occurred terminally. The "attacks" in Kahler's (1889) patient were probably due to anæmia and those in Case 11 of Davison and Balser (1937) to uræmia.

Diabetes insipidus.—This is a distinctive feature in a few cases and can be conveniently dealt with here. Meyer (1913) incriminated hydrocephalus as the ætiological condition whereas Denker and Brock (1934,

Case 1) and Bach and Middleton (1931) considered that lesions in the hypothalamic or pituitary regions were responsible. The latter hypothesis seems to be the more likely for in three cases of myeloma (Aronsohn, 1931: Bach and Middleton, 1931: Christophe and Divry, 1940, Case 2) there were lesions in the sellar region of the skull. Similarly, in Hand-Schüller-Christian's disease and sarcoidosis it is thought that the diabetes is produced by basal tumours or infiltration. It is to be noted, however, that myelomatous infiltration of the neurohypophysis found by Coste, Delbarre, Tissier and Sors (1948) and Piney and Riach (1931, Case 1) did not produce diabetes insipidus. The only account of hypothalamic changes in myelomatosis is that of Smereker (1951) who correlates them with disturbances of protein metabolism and does not mention diabetes.

The oft-quoted case of Anders and Boston (1903) is not included, for it is likely that the polyuria was due to renal changes. Renal functions were not investigated in any of the above 5 cases, nor was treatment reported. It is thus impossible to exclude the rare "water-losing nephritis" which is difficult to distinguish from diabetes insipidus clinically and which has been observed in a case of multiple myeloma (Roussak, 1953).

Mental changes.—As a terminal event, confusion, disorientation and drowsiness are not uncommon and are related to anæmia and toxæmia. Specific mental disorders, however, do not occur with myeloma and the psychosis of Davison and Balser's (1937, Case 5) patient was probably coincidental, as was, certainly so in the cases of Branham and Lewis (1921) and Armstrong *et al.* (1946).

Diagnosis.—This is not usually difficult because other features of myelomatosis are frequently present. "Solitary" myelomas as the only evidence of myelomatosis are rare and must be carefully differentiated from osteolytic metastatic deposits, especially as their age incidence is similar and on rare occasions the latter may produce Bence Jones proteinuria (Pines and Pirogowa, 1928). A meningioma may simulate a myeloma as is pointed out by Cushing and Eisenhardt (1938) and the eosinophilic granuloma has several features in common. Examination of the earlier literature shows that the skull sarcoma produced considerable confusion, but this should not be the case today. As with other intracranial myelomas, the ultimate diagnosis is by biopsy and by a search for myelomatosis.

(*B*) *Cases Without Myelomas of the Skull*

A myeloma growing from intracranial structures other than bone and convexity dura mater, is the rarest type that affects the brain and it produces the clinical picture of a non-specific, space-occupying lesion. There is only one instance of this in the literature (French, 1947) where the extra-osseous "plasmacytoma" was in the hypothalamus. Investigations were not complete, however, so that the generalized disease cannot be excluded confidently. Moreover, the tissue of origin was not discovered.

Case 3 is the second example.

Case 3.—Female, 58 years. One-and-a-half to two years of intermittent occipital headache worse for three months and with vomiting, drowsiness and periodic breathing. Signs of increased intracranial pressure and minimal left arm weakness and hypertonia. B.P. 190/110 and heart enlarged. Ventriculogram and operation revealed an extracerebral plasma cell myeloma of the dura of the tentorium cerebelli. Death. Autopsy. No other evidence of myeloma.

Miss W. M. U. (N.H. No. 32516) a school teacher aged 58, was admitted to the National Hospital, on July 25, 1951, under the care of Dr. J. St. C. Elkington. Her past and family histories were not relevant. For two years she had experienced intermittent occipital headaches, diagnosed as migraine and treated as such with relief. However, three months before admission these headaches became more severe and about six weeks before she had a severe stabbing pain in the right temporal region spreading to the occiput. Over a few days this pain subsided but did not disappear and five or six days later it again grew worse and was now accompanied by vomiting, drowsiness and Cheyne-Stokes' respirations. Again improvement occurred but there were a further two spells of head pain before the final episode three days prior to admission, when she was, in addition, confused and semiconscious.

Examination.—She was very drowsy, but could be roused to answer questions. There was well-marked Cheyne-Stokes' breathing. The optic discs were bilaterally swollen to an equal degree and there were arteriosclerotic changes in the retinal blood vessels. The visual fields seemed to be full to menace. The left pupil was slightly larger than the right, but its reactions were normal. In the left arm there was hypertonia and slight distal weakness, but the motor functions of the left leg were intact. The tendon reflexes were brisk and equal and the plantar responses flexor. The rest of the central nervous system was normal, as were the other systems except for a blood pressure of 190/110, and some enlargement of the heart, confirmed by X-ray.

Investigations.—X-ray of the skull showed only erosion of the dorsum sellæ due to raised intracranial pressure. *Electroencephalogram* (Dr. W. A. Cobb) was thought to be consistent with a right frontal tumour either large and infiltrating or surrounded by widespread œdema. *Ventriculogram* July 26, 1951 (Mr. L. S. Walsh). The septum pellucidum was shifted 1 cm. to the left and the floor of the right occipital horn was elevated, indicating a right-sided, temporo-occipital space-occupying lesion.

First operation, July 26, 1951 (Mr. L. S. Walsh).—Through a right temporal burr-hole and at a depth of 4 cm. a brain canula encountered abnormal tissue, which Dr. W. Blackwood thought was typical of a plasma-cell myeloma.

Further investigations.—X-rays: Unfortunately she was too ill to be X-rayed further, but a review of the skull and chest films showed no myelomas. *C.S.F.:* 3 cells, 50 mg. protein, Lange no change, W.R. not done. *Blood:* Hæmoglobin 108 per cent, red cells 5·34 million, white cells 6,200 (differential count normal). *Serum proteins:* Total proteins: 7·3 grammes per 100 ml., albumin 4·1 grammes per 100 ml. (gamma globulin: 1·7 grammes per 100 ml.), total globulin 3·2 grammes per 100 ml., A.G. ratio: 1·3 : 1.

Second operation, July 30, 1951 (Mr. W. McKissock).—A reddish-coloured extracerebral tumour which appeared to be arising from the floor of the middle fossa and extending towards the free edge of the tentorium was seen and its removal begun. The deepest part of the tumour had to be left because of troublesome

hæmorrhage, but 6·26 grammes were extracted. She remained deeply unconscious and died thirty-six hours after the second operation.

Post-mortem report (Dr. W. G. P. Mair).—*Skull:* the cranium was normal except for the operation flap, and after the dura had been removed the bones of the base were seen to be healthy and contained no myelomas. *Dura mater:* On the convexity, apart from surgical trauma, the dura mater was normal, and likewise at the base except for the right half of the tentorium cerebelli. Most of this had been removed at operation, and only the thickened medial part comprising the free edge remained, to which was fixed a small portion of the tumour that had been left behind at operation. *Brain:* There was no evidence of tumour tissue having invaded the brain. The right cerebral hemisphere was considerably swollen, and there was mid-brain distortion and herniation of cerebellar tonsils. Except for the heart, which was slightly enlarged, other organs and tissues were normal. There were no myelomas of the lumbar vertebræ, femora or humeri.

Histology.—The biopsy diagnosis of plasma-cell myeloma was confirmed (fig. 3). The cerebral tissue adjoining the lesion was normal, and so were all other structures examined. Several samples of bone-marrow from a number of bones were normal and there was no plasma-cell infiltration of the petrous bone.

Comment.—This was a most unusual case. There were no clues to the pathology of the tumour until the biopsy examination. The myeloma arose from the right half of the tentorium cerebelli and extended medially up to the free edge. It was impossible to say from which layer of dura mater it had arisen, but the bulk was growing from the superior surface and had no dural covering. Despite the latter, there was no actual invasion of brain tissue. Thus, whereas in French's (1947) case the tissue of origin is unknown, in Case 3 it was the dura mater. Unfortunately investigations during life to detect further evidence of a myelomatous process were not extensive but, at autopsy, investigations were negative. As the bone-marrow, however, was not fresh when examined, abnormalities cannot be entirely excluded. There is no doubt that the tumour was a true plasma-cell myeloma and as far as can be ascertained it was solitary at the time of the patient's death. However, it is possible to speculate that her early death was due to the situation of the tumour, and had it been in a less nocuous position she may have survived to develop further evidence of the disease later.

Group III.—Intra-orbital Tumour Syndromes

The orbit may be invaded by a myeloma and on rare occasions this may be the initial feature of multiple myelomatosis. These cases have been dealt with elsewhere (Clarke, 1953). Their incidence in multiple myeloma is impossible to discover for authors surveying large series have not remarked upon them. A plasma-cell myeloma, however, is one of the rarest orbital neoplasms for Offret (1951) found only 2 among 676 cases.

It is possible to divide examples of this lesion into (A) primary and (B) secondary, although the distinction is not always a definite one.

(*A*) *Primary Myeloma of Orbit*

Pathology.—The tumour in these cases grows either from the orbital contents or walls and the clinical picture is that which would be produced by any tumour of the orbit. There are in the literature at least 14 examples (Clarke, 1953) and each is a true plasma-cell myeloma; differentiation from the plasma-cell granuloma ("plasmoma" or "plasmocytoma") which grows from ocular structures is important but usually not difficult.

Clinical features.—Symptoms such as unilateral ocular prominence, decreased vision or diplopia are the first manifestations and proptosis, visual impairment or even blindness, papillœdema, pupillary changes and restricted eye movements, the abnormal findings. This clinical picture may precede other evidence of myelomatosis by several months (average of 8 in this series) but when generalization of the disease occurs, a fatal termination is rapid. The average survival was fifteen months.

(*B*) *Secondary Myeloma of Orbit*

Pathology.—Here, the myeloma grows from near-by bone, paranasal sinuses or nasal cavities to encroach upon the orbit secondarily. Although in some cases it may be difficult to ascertain from which structure the tumour originated, especially if it is advanced in growth when first seen, the history is often helpful.

Myeloma of the bone.—A typical case is that of Pages, Betoulières, and Cazaban (1952) where the myeloma was initially in the temporo-frontal region of the skull. As has been mentioned, basal myelomas (Group I) may extend into the orbit and produce complex clinical pictures. Lecène (1919), Lapointe (1929) and Gerèb and Könyves-Kolonics (1950, Case 1) have described cases with primary involvement of the frontal bone and Case 4 is a further example.

Case 4[1].*—Female, 60 years. Headache for nine months following left frontal injury. Left frontal tumour with left ptosis and proptosis for three to four months. Biopsy revealed myeloma. Bence Jones proteinuria. Parietal removal with development of coma and right hemiplegia not influenced by decompression. Death. Autopsy. Myeloma involving sinuses and orbital roof.*

Mrs. L. C., a housewife aged 60, was admitted to the London Hospital on March 24, 1938, under the care of the late Sir Hugh Cairns. She had suffered no previous illnesses of note and there was no significant family history. Nine months before admission she had fallen and struck the left side of her head but had not lost consciousness. Thereafter, she suffered headache which was mainly left frontal and which became progressively more severe. For three to four months there had been a swelling of the left forehead, slight prominence of the left eye, and drooping of the left eyelid.

Examination.—A slightly obese, cheerful woman of good general condition. A tender, cystic mass occupied the left frontal bone, extending down to involve the orbit. A distinct systolic bruit, which could be obliterated by pressure on the

[1]Case 2 of Clarke (1953).

homolateral carotid artery, was heard over it, and the irregular edge of a cranial defect could be felt beneath. There was slight proptosis and ptosis on the left, and a fullness above the eye. Visual acuity was normal. Both optic discs were myopic, and the left pupil was slightly smaller than the right, but it had normal reactions. Upward and lateral movements of the left eye were restricted. The central nervous system and other systems were normal.

Investigations.—X-rays of skull showed extensive destruction of the left frontal bone. X-rays of chest and long bones were normal. *Cerebrospinal fluid:* Pressure 140 mm., 1 cell, protein 25 mg. per cent. Lange no change, W.R. negative. *Blood:* Hæmoglobin 94 per cent, white cells 8,960 (differential count normal). *Urine:* Bence Jones protein present. *Biopsy* March 30, 1938 (Mr. J. B. Pennybacker): The tissue removed from the skull was reported by Professor D. S. Russell as "a myeloma of a plasmacytoma type" (fig. 4).

First operation April 5, 1938 (Sir Hugh Cairns and Mr. J. B. Pennybacker).—The tumour, although a product of the bone, was firmly attached to the dura mater which was intact except for two areas at the centre where nodules of tumour tissue had extended through it. One of these was 2 cm. in diameter but neither was invading the brain itself. An attempt was made to remove the tumour, but partly because of its vascularity (ligation of the ipsilateral common carotid artery did not help) and partly because of its adherence to the dura, this was only partially successful.

Progress.—The following day she was comatose and had a right hemiplegia, and as there was no improvement, a second operation was carried out two days later. The left frontal lobe was very œdematous and a portion of it was removed. There was some temporary improvement, but she did not regain consciousness and died two days later.

Autopsy (J. R. C.).—The remnants of the myeloma were found and tumour tissue had invaded the left frontal, left ethmoidal and the right frontal sinuses. There was a defect in the roof of the left orbit, with growth on the surface of the orbital fascia. Macroscopically the bone-marrow was normal in the sternum, vertebræ, one humerus, ribs and other bones, and no other abnormal features were detected.

Comment.—In this case, the myeloma grew from the frontal bone and involved the orbit secondarily. The precipitation of symptoms by trauma is interesting to note, for Geschickter and Copeland (1928) found a similar correlation in 20 per cent of their 425 cases. The cranial myeloma was single but the presence of Bence Jones proteinuria gave evidence of a more generalized process. Investigations during life were not extensive and post-mortem examination revealed no other tumours. However, as Northfield and Russell (1951) have pointed out, the bone-marrow in this case was not examined microscopically. It was considered that surgical removal of the tumour was justified, but the difficult operation illustrates the hazards of attempting complete excision of these tumours, which in this instance would not have been possible.

Myeloma of the mucosa.—True plasma-cell myelomas of the nasal and sinus mucosa may grow into the orbit, as has been described by Fuerste and Zuckerman (1950), the structure of origin in this case being the maxillary antrum. Intracranial extension produced terminal meningitis in a similar case (Pallestrini, 1927).

Clinical picture.—By noting the first symptoms, it is often possible to

determine the tissue from which the secondary myeloma originated, although the practical value of this knowledge is limited. Thus, in the first type it is a swelling of the bone near the orbit and in the second, symptoms referable to the nose or sinuses initiate the disease. Ocular features then develop. All of these patients mentioned were suffering from verified myelomatosis and their course was much as is usually seen in this disease, the survival being about eighteen months.

Treatment

Unfortunately, the course of multiple myelomatosis is not markedly influenced by treatment. Medical measures, which include urethane, stilbamidine and other histiotoxic drugs, can only be expected to produce symptomatic relief. Urethane, if tolerated by the patient, appears to be the drug of choice at the moment (Luttgens and Bayrd, 1951). Blood transfusions to combat the anæmia that frequently accompanies the disease, narcotics for pain and a diet high in calcium and phosphate and vitamin D are usually helpful. Radiation therapy has been employed with some improvement due to relief of local symptoms, especially pain, but the ultimate outcome of the disease is unlikely to be affected. The remissions sometimes observed may also occur in untreated cases. Surgery, excluding that at times necessary for biopsy, is rarely indicated and would only be considered in cases where the lesion was apparently solitary and readily accessible, or the progress of the disease was very slow.

Considering the cases with cranial nerve syndromes (Group I), only 14 of the 25 cases were treated. The effects of medical therapy could not be evaluated and operation when attempted resulted in 5 deaths among 8 patients. One gains the impression that those given irradiation made better progress but the follow-up has not been adequate nor the number of cases large enough. In addition, the cases that benefited most (e.g. Case 1) were of the slowly progressive type, so their response to therapy must be evaluated with caution.

Only 3 patients in Group II with cranial myelomas (Villata, 1928; James and Turner, 1952; Case 2) were treated, but experience with "solitary" cranial myelomas without intracranial complications, suggests that radiation therapy is the best form of treatment. In selected cases, local excision may be of value in rapidly relieving intracranial encroachment but because of the vascularity of the tumour, it is often a hazardous procedure. If the myeloma is intracranial as in Case 3, it must be treated in the manner of a cerebral tumour with operative removal, if accessible, and irradiation.

An orbital myeloma (Group III), if primary, and if the disease is neither widespread nor rapidly progressive, may occasionally be excised, although rarely completely, and then given local radiation therapy. Often, however, extension has occurred beyond the orbit, and, in common

with the cases of secondary orbital myeloma, palliative therapy only can be given.

The ultimate fate of the patient with a cranial or intracranial myeloma is determined by the behaviour of the disease as a whole, but in those cases where this lesion is alone producing symptoms, and the progression of the disease is slow, the neurological manifestations may warrant active therapy, as in the cases of myelomatous spinal cord compression.

Conclusions

(1) Although neurological complications of multiple myelomatosis are common, brain and orbital involvement is rare, despite the frequency of cranial lesions.

(2) The plasma-cell myeloma grows only from bone, dura mater or adjacent mucous membrane and cerebral and orbital structures are affected secondarily.

(3) Distinctive clinical pictures are thereby produced, depending upon whether cranial nerves, cerebral hemispheres or orbit are involved.

(4) It is unlikely that a "solitary" myeloma ("plasmacytoma") exists, for these tumours are but a stage of multiple myelomatosis.

(5) Treatment of these special cases is just as unsatisfactory as in other forms of myelomatosis.

Summary

(1) Cases of cranial or intracranial myelomas with neurological features have been collected and, together with 4 illustrative cases, they have been separated into three clinical groups.

Group I.—Cases with single or multiple cranial nerve palsies, caused by a myeloma of the bone of the skull base (Case 1).

Group II.—Cases simulating intracranial space-occupying lesions. (*a*) Cranial or dural myeloma with intracranial extension. Cases featuring increased intracranial pressure, focal symptoms and signs (Case 2), epileptic seizures, diabetes insipidus and mental changes are discussed. (*b*) Intracranial myeloma. There is one case from the literature, where the tissue of origin is unknown, and Case 3, with a myeloma of the tentorial dura mater.

Group III.—Cases with orbital involvement, either primary or secondary, which present as tumours of the orbit. In the former, the myeloma grows from the orbital contents or walls, but in the latter from adjacent bone (Case 4) or nearby mucosa.

(2) Treatment of these cases is considered and found to be, on the whole, unsatisfactory.

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CARCINOMATOUS NEUROPATHY AND MYOPATHY
A CLINICAL AND PATHOLOGICAL STUDY[1]

BY

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INTRODUCTION

THE association of neurological syndromes with carcinoma in the absence of relevant secondary deposits has apparently been recognized for many years. Several of the older textbooks of neurology mention carcinoma or carcinomatous cachexia as a cause of polyneuritis. The most interesting of these references is that of Williamson (1908); in discussing posterior column degeneration secondary to changes in the fibres of the posterior nerve roots he stated that "others have recorded these changes in cases of cachexia associated with cancer of various organs." More recently several examples of subacute cerebellar degeneration accompanying carcinoma have been recorded (e.g. Casper, 1929; Parker and Kernohan, 1933; and Greenfield, 1934), whilst Parkes Weber and Hill (1933) described the association of polyneuritis with carcinoma of the lung in one patient. Nevertheless it is only in the past few years that the connexion of these neuropathies with carcinoma has received much comment; the publications of Denny-Brown (1948) and Russell Brain, Daniel and Greenfield (1951) have been of particular importance in drawing attention to this association. The sites of the related carcinomata are varied; where the clinical picture has been that of subacute cerebellar degeneration lung, breast, ovary and uterus have been implicated (Brain *et al.*, 1951); but when the picture has been one of sensory neuropathy (Denny-Brown, 1948) or polyneuritis (Lennox and Prichard, 1950) the accompanying carcinoma has been found only in the lung with the exception of Dodgson and Hoffman's (1953) case of sensory neuropathy occurring with carcinoma of the œsophagus.

In this communication we present a clinico-pathological study of 19 patients in whom various neurological disorders have arisen in conjunction with carcinoma. Post-mortem examinations have been made within the hospital in 10 cases, and these have confirmed that the neurological manifestations under review have not been due to secondary deposits;

[1]Based on a communication to the Association of British Neurologists, February 1952.

in the other cases it has been considered that secondary growth could be excluded on the clinical findings and course of the disease. One of us has already published a brief account of some of our findings (Henson, 1953).

Material and Incidence

All our patients have been seen at The London Hospital, or in private neurological practice, and all save one were admitted to the hospital. 12 patients were referred directly for neurological opinion by their own doctors, the remaining 7 being examined at the request of colleagues at The London Hospital. 17 suffered from carcinoma of the lung and 1 each from carcinoma of the breast and ovary. There were 5 females and 14 males.

The first patient was seen in 1940 and the remainder between 1946 and June 1953. We have examined all but 3 (Cases 4, 13 and 14). In order to ensure that no cases have been missed the records of the Bernhard Baron Institute of Pathology were investigated for the fifteen-year period 1936–1950. The clinical notes and post-mortem reports were studied in all patients who died from carcinoma and were examined post mortem. There were 1,073 cases, including 224 patients with carcinoma of the lung. No further examples of carcinomatous neuropathy were discovered. A survey of all cases of polyneuritis admitted to the hospital in the same period was also made with negative results.

It is difficult to assess the frequency of neuropathy in patients with carcinoma from our highly selected material. Our figures are only large enough in the case of bronchial carcinoma to be worthy of record. In the years 1940–52 inclusive 1,309 cases of bronchial carcinoma were admitted and of these 15 (1·1 per cent) are known to have had neuropathies. During the years 1940–45 there was only 1 such patient (0·4 per cent) amongst 246 cases of lung cancer; however, during this period neurological cases were generally admitted to Chase Farm Hospital on account of the war. In the years 1946–52 there were 14 examples of neuropathy (1·3 per cent) in a total of 1,063 cases of bronchial carcinoma. There were 276 necropsies on patients with lung carcinoma during the seventeen years 1936–52 and these included 6 with neuropathy (2·2 per cent); 5 of these necropsies were performed in 1950 and 1951. Whilst it is likely that some cases of carcinomatous neuropathy were misdiagnosed in earlier days, the symptoms being attributed to secondary deposits or coincidental disease, it seems certain that some of the manifestations at least are new and that the condition as a whole has increased considerably in frequency.

The clinical manifestations of these neuropathies are varied; patients frequently show clinical and pathological evidence of multiple lesions in the nervous system. The general term "carcinomatous neuropathy" has therefore been employed in diagnosis. Our clinical material includes

examples of subacute cerebellar degeneration, sensory neuropathy, polyneuritis and neuromuscular disorders (motor neuropathy and myopathy). In the clinical histories which follow similar cases are grouped together ; thus Cases 1 to 5 had cerebellar disorders, Cases 6 to 8 sensory neuropathy, Cases 9 to 11 polyneuritis and Cases 12 to 19 unusual neuromuscular disorders. Nevertheless we have avoided rigid classification, for although some of our patients have manifested a pure system lesion the clinical picture has usually been mixed.

Case Histories and Pathology

Case 1.—*Female, aged* 59. *Admitted to The London Hospital, July* 21, 1948. (*L.H. No.* 41144.)

Six months previously she began to feel giddy, sometimes with nausea and vomiting. This became so severe that in one month she was unable to walk without support. At this time she developed double vision and rapidly progressive weakness of the legs so that in another month she was unable to walk at all. Weakness and tremor now appeared in the right upper limb ; the tremor later spreading to the other limbs. At the time of admission she was bedridden with paralysis of the lower limbs, severe weakness of the right upper limb and slight weakness of the left. There was some difficulty in initiating micturition. She also complained of occasional frontal headaches and paræsthesiæ all over her body. She had been receiving 3 grains of thyroid extract daily for many years on account of myxœdema.

On examination she was a thin woman with myxœdematous facies and generalized ichthyosis. A small, hard, irregular mass of glands was palpable in the right axilla. The breasts were normal. She was euphoric and mildly demented. The right pupil was slightly larger than the left, but the pupillary reflexes were normal. There was a slight right ptosis and lateral strabismus. The external ocular movements were full except that on conjugate upward movement the right eye deviated laterally. There was diplopia on looking upwards and to the right. She had coarse rotary, lateral and vertical nystagmus. The jaw-jerk was grossly exaggerated. The palate deviated to the left and the tongue was protruded to the right. There was dysarthria of cerebellar type. There was generalized muscular wasting without fasciculation. The limbs were generally hypotonic but flexor spasticity was noted at the right elbow and there were contractures of both tendo Achilles. There was generalized weakness of the upper limbs, severe on the right and slight on the left, with gross cerebellar ataxia. The lower limbs were almost completely paralysed. A coarse irregular tremor affected the upper limbs at rest whilst the legs were occasionally involved on voluntary movement. The tendon reflexes were all grossly exaggerated, right more than left in the arms, the superficial abdominal responses were absent and the plantar responses were extensor. Sensation was entirely normal. The other systems were clear. The blood pressure was 160/110, falling to 120/80 later in the illness.

X-rays of the chest, skull and spine were normal. A barium enema was negative. The C.S.F. contained 90 mg. per cent protein and 20 cells, predominantly lymphocytes, per c.mm. Culture was sterile. The W.R. was negative in blood and C.S.F., Lange curve 223321. Biopsy of the enlarged axillary glands showed diffuse infiltration with solid, polygonal-celled carcinoma. Lumbar puncture on August 12, 1948, showed a normal fluid, 20 mg. per cent protein and 1 cell per c.mm.

Within three weeks of admission the cerebellar signs in the limbs began to give way to an intense spasticity, affecting the right upper and both lower limbs, with only slight involvement of the left arm. This process continued until by

January 1949 there was no trace of cerebellar deficit in the limbs and the static tremor had disappeared. Her diplopia had also gone, but objectively the abnormalities in the cranial nerves were unchanged. The right upper limb was severely paralysed in flexion, and there was advanced paraplegia in extension. The left upper limb was slightly spastic and weak but function had improved with the disappearance of ataxia. With the development of spasticity the tendon reflexes became less brisk, but otherwise the reflexes were unchanged. Examination of the C.S.F. on October 2, 1948, showed 40 mg. per cent protein and 3 cells per c.mm.

A small lump was found in the right breast in January 1949. On removal this proved to be a solid, trabecular, polygonal-celled carcinoma. The last three months of life were punctuated by episodes of bladder and pulmonary infection, chronic constipation with abdominal distension and transient œdema of the legs. There was no further significant alteration in the neurological state. She died on April 10, 1949.

Pathological Examination

Summary of necropsy (*P.M.* 125. 1949). *Myxœdema. Atrophy and fibrosis of thyroid. Secondary carcinoma of right axillary glands.*

Apart from confluent secondary growth in the right axilla and a small deposit in a right supraclavicular gland there were no further metastases in the body. Fibrotic thyroid (5·4 grammes) containing a few pink nodules (0·15 cm.) of thyroid tissue. Scanty pubic and axillary hair. Considerable pitting œdema of feet, legs and lumbar region; less of thighs; none of face, neck or shoulders. Remaining endocrine glands macroscopically normal. Atrophy of heart. Considerable general atheroma. Chronic purulent cystitis. Great dilatation of large intestine, especially of pelvic colon. Slight convolutional atrophy of frontal poles of cerebrum; no further visible abnormality in central nervous system. A moderately nourished woman.

Microscopic examination.[1]—*Thymus:* Scanty trabeculæ of glandular tissue; mainly adipose. *Thyroid:* Extensive replacement by fibrous tissue; scattered foci of degenerating acini, some showing squamous metaplasia; focal lymphocytic infiltration. *Brain:* The right motor cortex is normal. In the frontal cortex there is focal gliosis in the deep layers but no neuronal changes. There is a well-defined inflammatory and degenerative process in the subthalamic nuclei. In these the neurones are in stages of chromatolysis, which is often severe. Knots of microglial cells represent sites of neuronophagia. The regional blood-vessels are in places cuffed with lymphocytes, and numerous foam-cells are distributed near the borders of the nuclei. There is reactive gliosis. There is also active degeneration of the strio-Luysial fibres.

An arteriole at the junction of the right globus pallidus and putamen is cuffed with lymphocytes. At the same site on the left is a similar vessel accompanied by two clusters of microglial cells in the adjacent nervous tissue.

Mid-brain. Pons. Medulla: In the tegmental part of the brain-stem there is again occasional cuffing of the perforating vessels and a patchy degeneration of occasional neurones resulting in aggregates of microglial cells from neuronophagia. The oculomotor nuclei are intact. At the junction of the substantia nigra and crura cerebri the vessels are slightly cuffed.

Cerebellum: In the superior cerebellar peduncles there is a conspicuous symmetrical area of degeneration, with partial demyelination. A frozen section from this area on one side contains many fat-granule cells. There is patchy

[1]Both here and in subsequent reports histological observations on various tissues are omitted when they are deemed irrelevant.

degeneration of the dentate nuclei with evidence of neuronophagia and perivascular cuffing as in the subthalamic nuclei.

In the cerebellar cortex occasional Purkinje cells have disappeared but the remainder are well preserved. In other respects the appearances are normal.

Spinal cord : At all levels, but particularly in the cervical and lumbar enlargements, the anterior horns show some loss of neurones and stages of chromatolysis in others, though many are well preserved. There are also foci of round-cell infiltration with lymphocytes and microglial cells, apparently at sites where neurones have disintegrated (fig. 1). The regional blood-vessels are occasionally cuffed with lymphocytes, and there is diffuse gliosis accompanied by an excess of microglial cells. The anterior horns are bordered by crescentic areas of partial demyelination in the antero-lateral columns of white matter, but these do not involve the pyramidal tracts (fig. 2). Foam-cells are conspicuous, especially at the junction of these areas with the anterior horns. Cuffing of vessels in the white matter is confined to the areas of degeneration. There is no meningitis and the posterior horns appear normal.

Peripheral nerves : The right anterior tibial, right and left median nerves show stages of Wallerian degeneration which are scantier in the former than in the latter. The right radial nerve, taken from the forearm, is normal.

Muscle : A portion of tibial muscle appears normal.

Case 2. *Female, aged* 56. *Admitted to The London Hospital, October* 2, 1950. *L.H. No.* 41304/50.)

For two years she had been losing weight and lacking energy. Eighteen months before admission she began to suffer from dysphagia, mainly towards the end of a meal ; this symptom cleared after a while. For one year she had noticed increasing weakness of the legs with accesses of weakness in which she could hardly walk. There were severe cramp-like pains in the calves. Eight months before she was first seen, and five days after a hæmorrhoidectomy in another hospital, she developed a complete right ptosis, slurring and weakness of her voice and her dysphagia returned. The ptosis was variable, sometimes both lids were affected, at other times the right or left might be involved ; it was always worst at the end of the day. Eventually a moderate left ptosis became established. Meanwhile the weakness and cramps in the legs increased and the disturbances of voice and swallowing persisted.

Examination revealed an ill, wasted woman, who could walk only with support. She was anxious and forgetful. There was a moderate left ptosis but no pupillary abnormality. Elevation of the right eye and elevation and depression of the left eye were defective, but there was no diplopia. There was slight nystagmus to the right. Facial and palatal movements were weak bilaterally. Her voice was nasal, dysarthric and rather hoarse. There was generalized hypotonia of the limbs, though ankle clonus was present, with wasting and weakness. The trunk was also weak. No fasciculation was seen. There was a little cerebellar ataxia of the left upper limb. The arm and ankle jerks were sluggish and equal, the knee-jerks being only obtainable on reinforcement. The plantar responses were extensor. The calves were tender but there was no sensory loss. Scattered rhonchi were heard in the chest and movement was diminished at the right base. Blood pressure 120/70.

An initial chest X-ray was negative, but following a pulmonary infection shortly after admission to hospital radiographic evidence of collapse of the right lower lobe was secured. Bronchoscopy and biopsy revealed the presence of an inoperable oat-celled bronchial carcinoma. Barium swallow gave no evidence of œsophageal obstruction. The C.S.F. contained 45 mg. per cent protein and 2 cells

per c.mm. Lange curve 222110. The W.R. was negative in blood and C.S.F. The administration of 2·5 mg. of neostigmine subcutaneously did not ameliorate her weakness.

She was treated with aneurine, riboflavine, nicotinic acid and vitamin capsules (N.F.) without relief. She complained bitterly of pains and cramps in her limbs. The weakness of limbs and trunk progressed. Dysphagia rapidly became complete in the last few days of life. She died on December 9, 1950.

Pathological Examination

Summary of necropsy (*P.M.* 444. 1950). *Purulent bronchitis. Primary carcinoma of right lung.*

Carcinoma (8 × 9 × 6 cm.) arising from main bronchus to lower lobe, extending along its branches and into hilar glands and glands at bifurcation of trachea. Invasion by growth of œsophagus with ulceration of mucosa and stenosis. No remote secondary growth. Endocrine glands normal. Dilatation of large intestine. No visible abnormality in central nervous system apart from a few small cystic areas in lenticular nuclei and external capsule. A pale, wasted woman.

Microscopic examination.—The neoplasm in the lower lobe of the right lung is an anaplastic carcinoma composed of small polygonal and oat-cells. The thymus is composed of adipose and fibrous tissue, one minute island of glandular tissue being present.

In the *thyroid* some acini are distended with colloid. Most are small, with severe degeneration and desquamation of the epithelium. There is considerable fibrosis and atrophy, with slight focal lymphocytic infiltration.

Central nervous system : No significant lesions appear above the level of the brain-stem. In the subthalamic nuclei there is slight chromatolysis only. In the nuclei of the oculomotor nerve there are stages of severer chromatolysis, with margination of the nuclei in some instances. Similar degeneration, with appreciable loss of neurones, is found in the nuclei of the ninth, tenth and twelfth nerves in the medulla oblongata. In the corresponding nerve roots many fibres are lost, with condensation of the collagen. Both here and in the pons there is slight perivascular cuffing with lymphocytes of a few blood-vessels in the tegmen. The cerebellum appears normal.

In the spinal cord there is slight lymphocytic infiltration of the pia mater in the lumbar region ; in a few places this also involves anterior and posterior roots. There is a deep zone of marginal pallor and vacuolation in the white matter of the lateral columns at all levels and, in the thoracico-lumbar cord, degeneration of both crossed pyramidal tracts, demonstrated by loss of myelin associated with large foam-cells and an excess of infiltrating mononuclear cells. Occasional perforating vessels in all columns of the white matter are thickly cuffed with lymphocytes at all levels, many being affected in some segments, notably in the cervical and lumbar enlargements. Stages of chromatolysis are evident in the anterior horns and, at some levels, definite loss of neurones. Thus in the sixth cervical segment a nodule of microglial cells (fig. 3) is indicative of neuronophagy. In the same segment there are a few foci of recent hæmorrhage, and some perivascular cuffing in the borders of the grey matter.

The anterior spinal roots show an uneven loss of myelinated fibres, with condensation of collagenous tissue (fig. 4). This varies in different segments. The posterior roots are normal.

The left Gasserian ganglion is normal and, in the posterior root ganglia examined, some degeneration of neurones accompanied by proliferation of capsular cells is seen. This is, however, slight.

Peripheral nerves : The right radial, right ulnar, right median, right sciatic and posterior tibial nerves show nothing significant.

Muscles : In the *levator palpebræ superioris* most fibres are grossly atrophied and many have lost their cross striation. In places the interstitial tissue appears expanded by œdema, and infiltration with small lymphocytes. The latter are not compact as in lymphorrhages. They also infiltrate occasional nerve-bundles. Extreme atrophy of the muscle fibres is found in parts of the *right abductor minimi digiti* though cross-striation is preserved. Other parts of the muscle show gradations in atrophy. There is no associated cellular infiltration. The *right pectoralis major* is less affected, but occasional fibres are greatly atrophied.

Bundles of nerve-fibres in the orbital and digital muscles show an uneven loss of axis-cylinders, and there is a loss of the nerve-filaments in the motor end-plates of atrophied fibres. A few motor nerve-endings, found on non-atrophied fibres, appeared normal. The preparation of pectoral muscle yielded no definite information by the Bielschowsky method.

Case 3.—*Male, aged* 56. *Admitted to The London Hospital, September* 30, 1950. (*L.H. No.* 39429/50.)

One month before admission he had an attack of giddiness and his walking became unsteady. Clumsiness of the arms, blurring of vision, dysarthria and dysphagia soon followed, whilst his gait rapidly became more ataxic.

On examination he had marked cerebellar dysarthria and extreme euphoria. There was slight nystagmus. The limbs were hypotonic and showed gross cerebellar ataxia, left more than right. Power was normal. The tendon reflexes were all present and equal. The right plantar response was flexor and the left extensor. His gait was wide-based and ataxic and trunk ataxia was very evident. No other abnormality was found in the nervous system or elsewhere. Blood pressure 140/90.

The C.S.F. was normal in every respect ; the W.R. was negative in blood and C.S.F. Chest X-rays revealed a small opacity in the anterior basal segment of the right lower lobe, visible only in the right lateral view. Bronchoscopy was negative. Chest exploration was deferred and he was allowed home. Further X-rays in December 1950 showed a slight increase in the size of the pulmonary opacity. Bronchoscopy was again negative but on January 29, 1951, a small, tubular, columnar-celled carcinoma measuring 3 × 3·5 cm. was removed by wedge resection of the lung. By this time his cerebellar ataxia had increased so that he was unable to walk without support, his speech was scarcely intelligible and he had diplopia and coarse lateral and vertical nystagmus. The knee and ankle jerks were exaggerated and equal and both plantar responses were extensor. He was even more euphoric and by now mildly demented.

Repeated examinations up to his death on August 5, 1952, revealed no further significant change in his neurological condition. Two further C.S.F. examinations were negative. Intellectual tests confirmed the presence of a moderate dementia. A small subcutaneous metastasis was removed from the abdominal wall in July 1951 and secondary deposits appeared in the cervical glands in February 1952, at which time he was shown to the Neurological Section of the Royal Society of Medicine at a clinical meeting. His general condition gradually deteriorated. He died elsewhere and no post-mortem was performed.

Case 4. *Male, aged* 65. *Examined May* 2, 1951.

In May 1949 he had developed pulmonary symptoms and excruciating pains in his limbs. In July 1949 an anaplastic carcinoma of the left lower lobe bronchus was removed surgically. Following this operation the pains disappeared. He suddenly became deaf in both ears in October 1949. In January 1950 his legs became weak, his feet felt cold and numb and the limb pains returned. At this time there

was an episode of diplopia lasting several weeks. In April 1950 his gait became unsteady, and he lost his balance on turning his head. He also had numbness of his left index finger, a swollen feeling in his lips and tongue and slight dysphagia. His condition grew steadily worse, but no clinical or radiological evidence of recurrence of growth could be found although he had a persistent cough.

On examination he had slight cerebellar dysarthria and bilateral deafness. There was weakness of conjugate lateral movement of the eyes but no nystagmus. The limbs were slightly wasted and weak peripherally. All tendon reflexes were diminished except the ankle-jerks which were lost. The plantar responses were extensor. Vibration sense was impaired below the knees. His gait was broad-based and ataxic. Blood pressure 140/80. The C.S.F. was completely normal.

He was treated with injections of liver extract without improvement. He became so ataxic that he was unable to stand, finally dying at home with evidence of pulmonary recurrence on August 2, 1951. No post-mortem was performed.

Case 5. *Female, aged* 48. *Admitted to The London Hospital, March* 26, 1953. (*L.H. No.* 11250/53.)

One year previously she had begun to have occasional brief attacks of giddiness. Six months previously the attacks became more severe and she developed progressive ataxia of the limbs. She also complained of diplopia and that objects would not keep still. Her limbs began to shake and jump involuntarily. Her speech became slurred.

On examination her mental state was normal apart from gross anxiety. There was dysarthria of cerebellar type and lateral nystagmus. Her limbs were grossly ataxic, so that she was unable to walk or feed herself. There was a continuous coarse tremor of the head and limbs. The tendon reflexes were brisk and equal and the plantar responses were equivocal. No other abnormality was found in the nervous system. Blood pressure 130/90. The C.S.F. contained 11 lymphocytes and 40 mg. per cent protein. Lange curve 012221. W.R. was negative in blood and C.S.F.

Her condition gradually deteriorated with increasing cerebellar ataxia and tremor. The plantar responses became frankly extensor. On April 13 vaginal examination revealed a small mass on the left side of the pelvis, and laparotomy (May 13, 1953) showed the presence of bilateral ovarian tumours with secondary deposits in the omentum. Histological examination showed the tumours to be papilliferous cystadeno-carcinoma. C.S.F. examination on April 14, 1953, showed precisely the same findings as before. Repeated examination on June 5, 1953, produced a fluid containing 20 mg. per cent protein and 1 cell per c.mm. Lange curve 012221. An electromyogram was normal and serial readings of plasm and red cell cholinesterase showed figures well within the range of normal.

Cerebral biopsy done on June 29, 1953, showed no obvious changes.

The patient remained orientated and fully accessible but became increasingly anxious; she moaned and screamed continually. For this reason a limited prefrontal leucotomy was carried out on June 29, 1953. This was effective in relieving her tension for six weeks only, and a standard leucotomy was performed on September 7, 1953. Heavy sedation with barbiturates, paraldehyde and morphia was also required. She died on November 9, 1953.

Pathological Examination

Summary of necropsy (*P.M.* 424. 1953). *Ascending purulent pyelonephritis. Secondary carcinoma of lymph glands. Old operation: excision of ovaries.*

Small nodules and plaques of secondary growth in peritoneum. Secondary carcinoma in iliac, para-aortic, mediastinal and a few cervical lymph glands.

One small secondary deposit in liver. Acute cystitis. Thymus replaced by adipose tissue. Endocrine glands normal. Incomplete occlusion of left renal vein by ante-mortem thrombus. Similar thrombus in left external iliac vein. Organized thrombus throughout right femoral vein. Firmly adherent ante-mortem thrombus in a branch of pulmonary artery to each lower lobe of lungs. Bilateral frontal operation-scars (leucotomy). Diffuse orange pigmentation of inner aspect of dura. Fibrous adhesion of dura to brain at leucotomy sites. Slight orange pigmentation of leptomeninges at base of brain and over temporal lobes. Slight convolutional atrophy of frontal poles. Considerable diffuse atrophy of cerebellar folia. On section after fixation: extensive asymmetrical necrosis (leucotomy) forming an irregular band traversing each frontal lobe. Diffuse congestion of brain but no metastases, and no further macroscopic abnormality in brain or spinal cord. A wasted woman.

Microscopical examination.—Sections of various organs provide no additional information apart from the presence of a few foci of chromophobe-cell hyperplasia in the pars distalis of the pituitary. A few cords and small islands of glandular tissue lie in the otherwise adipose thymus.

Central nervous system.—Brain: Apart from the traumatized areas in the frontal lobes there is no abnormality in the cerebrum. The subthalamic nuclei are unchanged. Pathological changes related to the carcinomatous neuropathy are restricted to the cerebellum. Here there is conspicuous diffuse atrophy of the cortex associated with loss of the Purkinje cells and, in places, some diffuse loss of granule cells. In Nissl preparations occasional Purkinje cells at wide intervals are found in stages of chromatolysis. There is multiplication of the astrocytes in this layer and obvious gliosis therefrom in the molecular layer, which is narrowed. Though this change is so widespread, affecting both the lateral lobes and vermis, one small area deeply situated in the right lateral lobe had escaped degeneration. With stains for myelin there is slight pallor of the white matter in a few lobules, and occasionally some fat granule cells where the loss of sheaths is greatest. These cells are abundant in a zone encircling the convexity of the dentate nucleus. Gliosis is conspicuous in and about the nucleus. Though there is some chromatolysis, with karyolysis and pyknosis, in the neurones there is no obvious loss of cells in this nucleus. The cerebellar peduncles are intact and the brain-stem normal.

Spinal cord: The representative segments examined are normal.

Posterior root ganglia from C8 and L3 are also normal.

Muscles: Portions of pharynx, soft palate, tongue, diaphragm, upper œsophagus, sternomastoid, subscapularis and abductor minimi digiti were examined. Changes were confined to the last four of these. In the upper œsophagus there is slight atrophy of occasional muscle fibres. In the other three muscles the atrophy is great, though somewhat uneven in the sternomastoid. Cross-striation is preserved. There are a few small foci of infiltration with plasma cells and lymphocytes in the interstitial tissue and, in the sternomastoid, an associated increase in collagenous fibres. Bielschowsky preparations revealed no abnormality in the included nerve fibres and their terminations.

Case 6.—*Male, aged* 52. *Admitted to The London Hospital, December* 21, 1947. (*L.H. No.* 520/48.)

Five months before he had a febrile illness with cough, hæmoptysis and low backache. He recovered in a fortnight. One month later his backache recurred, accompanied by tingling and pains in his limbs. There was also rapidly progressive weakness and ataxia of his limbs so that he was bedridden on admission.

On examination he was wasted and had early clubbing of the fingers. There

was generalized muscular wasting and hypotonia of the limbs with severe ataxia. Power was difficult to evaluate on account of hysterical overlay. The triceps jerks were just present, but all other tendon reflexes were absent. There was cutaneous anæsthesia and analgesia extending to the elbows and knees. Position sense was lost in the fingers and toes and impaired at the ankles, whilst deep pressure pain was diminished in the calves. Vibration sense was absent below the elbows and knees. No other abnormality was found in the nervous system. There were signs of collapse of the lower lobe of the right lung. Blood pressure 120/80.

The C.S.F. contained 60 mg. per cent protein and 1 cell per c.mm. Lange curve 011221. W.R. negative in blood and C.S.F. Radiological and bronchoscopic examination showed a carcinoma of the right lower lobe bronchus. Treatment consisted of deep X-rays to the affected lung, and thiamine, 5 mg., pyridoxin, 10 mg., and multivite tablets, all thrice daily. The neurological condition remained unaltered. He was discharged home on March 31, 1948.

He was readmitted on May 3, 1948. His general condition had improved sufficiently to permit radical surgery and right pneumonectomy was performed on May 20, 1948. Examination of the specimen showed secondary deposits of oat-celled carcinoma in a paratracheal lymph gland, but no neoplastic tissue was found in the excised lung, presumably because of the deep X-ray treatment. Re-examination of the nervous system showed no change except that the triceps-jerks had now disappeared.

He was again admitted on October 1, 1948. He had gained a stone in weight and felt much better. The pains in the limbs had disappeared following operation, but he was still bedridden because of his ataxia. The objective neurological state remained unchanged. The C.S.F. was now normal, protein 30 mg. per cent. Lange curve 000000. He was allowed home on October 23, 1948. At a final out-patient examination on January 25, 1949, metastases were discovered in the cervical glands and liver. X-rays of the chest showed a recurrence in the left lung. The neurological condition was unchanged. He died at home later in the year, the exact date being unknown. There was no post-mortem examination.

Case 7.—*Male, aged* 35. *Admitted to The London Hospital,* November 29, 1949. (*L.H. No.* 22730/49.)

Ten months before admission he had a febrile illness with pain in the left chest. X-rays taken after this illness, in May 1949, showed an opacity in the left upper zone. Bronchoscopy was negative. Physical examination of the chest and nervous system showed no abnormality.

For six months he had experienced a burning sensation over the soles of both feet and numbness of the right leg. Later the other limbs became numb. Three weeks before admission he developed hydrocephalic headaches and impairment of vision. Ataxia had developed insidiously from the outset. On admission he could just walk with a stick.

Examination revealed a wasted, ill man. Neck rigidity was present and he had bilateral papillœdema with hæmorrhages. There was coarse lateral and vertical nystagmus. There was generalized wasting and weakness of the limbs, most marked in the hands, with hypotonia and ataxia. His gait was grossly ataxic. All tendon reflexes were lost. The plantar responses were flexor. There was an ill-defined cutaneous sensory loss to pin-prick, heat and cold and light touch over the hands, forearms and lower limbs to the knees. Position sense was lost in the fingers and toes, but present at the wrists and ankles. Vibration sense was absent below the elbows and knees. The percussion note was impaired and air entry diminished over the left middle and upper zones. Blood pressure 160/70.

X-rays of the chest showed the opacity in the left lung to be rather smaller. Bronchoscopy was negative. The C.S.F. pressure was 300 mm., and the fluid

contained 160 mg. per cent protein and 2 cells per c.mm., Lange curve 112221 ; W.R. negative in blood and C.S.F.

It was evident that the patient was suffering both from a sensory neuropathy and cerebellar metastasis due to bronchial carcinoma. He died on January 5, 1950.

Pathological Examination

Summary of necropsy (*P.M.* 7. 1950). *Secondary carcinoma of brain. Primary carcinoma of upper lobe of left lung.*

Small primary carcinoma (about 0·7 × 0·3 cm.) under mucosa of anterior branch of axillary bronchus of left upper lobe. Secondary deposits in left hilar glands, but none elsewhere except in brain. Back-pressure congestion of liver, spleen and kidneys. No visible abnormality in endocrine glands. Secondary carcinoma (4·5 × 2 cm.) in right lobe of cerebellum, and (5 × 2 cm.) in right occipital lobe. Four additional small foci of secondary growth in cerebrum, and one in left lobe of cerebellum. Moderate dilatation of lateral and third ventricles. Considerable flattening from pressure of cranial nerves in right cerebello-pontine angle. Grey discoloration of posterior spinal roots, most marked in cauda equina, and diminishing towards cervical cord. Creamy-white opacity of posterior columns, on transverse section, throughout spinal cord. A spare well-developed rather small man.

Microscopical examination.—Lung : Diffuse infiltration of wall of bronchus by small polygonal and oat-celled carcinoma. Similar carcinoma in adjacent lymph-node.

Brain : Similar carcinoma in both lobes of cerebellum, the right occipital and parietal lobes. Focal carcinomatous infiltration of leptomeninges over upper part of vermis ; in the subjacent cortex there is occasional loss of Purkinje cells, great œdema and slight focal infiltration of the molecular layer with polymorphonuclear leucocytes. There is no further carcinomatosis of the meninges at any level examined.

The right basal ganglia, sectioned in the coronal plane, are normal ; in particular the subthalamic nucleus is intact. Both the trigeminal and vestibular nerves show severe degeneration, with fragmentation of their myelin sheaths and axis-cylinders in their intramedullary course. Degeneration, with some gliosis and numerous foam-cells, affects the gracile and cuneate nuclei in conformity with a profound and diffuse degeneration throughout the posterior columns of the spinal cord (fig. 5). There is no shrinkage of the columns and, from the abundance of foam-cells, the degeneration is in a relatively early stage. There are no further changes in the spinal cord. The entering posterior roots are in stages of Wallerian degeneration. and this is most profound in the caudal segments becoming maximal in the first sacral roots (the most caudal examined).

Five *posterior root ganglia* were examined (C7, Th1 and 12, L4 and 5). Loss of neurones, with proliferation of the capsular cells to form "residual nodules" is a pronounced feature and is greatest in the lumbar specimens (fig. 6). In one only (lumbar 5) there is a focus of lymphocytic infiltration, apparently enclosing a degenerating neurone.

Peripheral nerves : The radial (axilla), ulnar and median (forearm), internal popliteal and tibial (at knee) and external popliteal nerves all show patchy loss of myelin and stages of Wallerian degeneration. The change is greatest in the median, ulnar and external popliteal nerves and is least in the radial nerve.

No muscles were examined in this case.

Case 8.—*Male, aged* 58. *Admitted to The London Hospital,* May 5, 1951. (*L.H. No.* 17882/51.)

One year previously he gradually developed pains, numbness and coldness throughout the lower limbs. Shortly afterwards the pains involved the arms and pins and needles affected the hands. There was loss of feeling in his fingers, which were very clumsy, and his gait became unsteady. Nine months previously he had been admitted to another hospital for investigation of hæmoptysis. X-rays of the chest revealed a left hilar opacity but bronchoscopy and biopsy were negative. The C.S.F. contained 110 mg. per cent protein but was otherwise normal. A further examination two months later showed a protein content of 60 mg. per cent. Fractional test meal showed a resting achlorhydria but a rapid response to histamine injection. His pulmonary symptoms progressed with hæmoptysis and pain. The further evolution of the neurological complaints is uncertain, though the sensory and motor disturbances persisted.

On examination he was a wasted, ill man. There was generalized hypotonia and wasting of the limbs with slight weakness and moderate ataxia, more marked in the legs. His gait was ataxic with marked hysterical overlay. The biceps and supinator jerks were present, right brisker than left; the triceps-jerks were diminished. The knee and right ankle jerks were sluggish and the left ankle-jerk was lost. The upper abdominal responses were brisker right than left, whilst the lower were absent. The plantar responses were absent. There was cutaneous sensory impairment of all modalities extending to the mid-forearms and mid-thighs. Position sense was impaired in the left fingers and all the toes. Vibration sense was lost below the level of the xiphisternum. The calves were tender. Blood pressure 130/70.

The C.S.F. was normal, protein content 30 mg. per cent. Lange curve 001100. The W.R. was negative in blood and C.S.F. After investigations had revealed the presence of a carcinoma of the left main bronchus thoracotomy was performed on May 12, 1951. An inoperable growth was found. The patient died on June 21, 1951, following a large hæmoptysis.

Pathological Examination

Summary of necropsy (*P.M.* 236. 1951). *Hæmorrhage into bronchi. Carcinoma of left lung. Old operation : Thoracotomy.*

Carcinoma (approximately 3 cm. diam.) arising from main bronchus to lower lobe with extensions along left bronchus to carina, bronchi to upper lobe and middle third of œsophagus. Fluid blood throughout all bronchi in both lungs. Firm growth uniting visceral and parietal pleura at site of thoracotomy, and surrounding left pulmonary veins. Secondary growth in left lower paratracheal glands, in cœliac glands and in lymph glands at cardiac end of lesser curve of stomach. No further secondary growth in body. Normal endocrine glands. No visible abnormality in brain. Conspicuous white opacity of posterior columns in lower thoracic segments of spinal cord, diminishing in lumbar and upper thoracic segments. Firm, white, miliary nodule on posterior root of first lumbar segment. A wasted man.

Microscopical examination.—The tumour in the left lung is a polymorphic-celled carcinoma of the bronchus.

No histological changes were found in the cerebrum or brain-stem. The cerebellum is normal apart from the loss of occasional Purkinje cells. Throughout the spinal cord certain areas of the posterior columns are partially demyelinated and contain many foam-cells. In tracing the degeneration upwards from the first sacral to the second cervical segments the distribution of the zones of degeneration in these columns corresponds to a selective involvement of the roots in the lumbar

and cervical enlargements, with sparing of the lower sacral and thoracic segments. There is slight perivascular lymphocytic infiltration in the median raphe, and about vessels in the posterior columns. The anterior horns are well preserved. The fibres of the posterior roots are in stages of Wallerian degeneration in C6, Th12, L2 and S1. The nodule on the lumbar root is a minute Schwannoma.

Posterior root ganglia (C3, C6, Th1, Th11 and L3 examined) : There is uneven degeneration of the neurones with proliferation of capsular cells and the formation of residual nodules. The severity of this degeneration is greatest in L3, and considerably less in C6, Th11, C3 and Th1 (in this order). There is no obvious change in the right Gasserian ganglion.

Peripheral nerves : The left ulnar, right sural, and posterior tibial were examined. All show patchy Wallerian degeneration, least developed in the ulnar nerve.

Muscles : Moderate atrophy of some bundles of fibres was found in the left flexor sublimis, and slight of groups of fibres in the left abductor minimi digiti. Cross-striation is well preserved. In the right gastrocnemius muscle there is generalized but uneven atrophy of fibres. Cross striation is good, but a very few fibres have become moniliform, are focally infiltrated with mononuclear cells and their myoglial fibrils are spirally arranged.

In the three orbital muscles examined (levator palpebræ superioris, lateral rectus and superior oblique) the histological changes present are within the range of normal for the age of the subject. In Bielschowsky preparations of all these muscles the intrinsic nerves and their terminations appear normal.

Case 9.—*Male, aged* 64. *Admitted to The London Hospital,* July 22, 1951. (*L.H. No.* 30109/51.)

He was admitted for investigation of rapidly progressive weakness of the legs of two weeks' duration. It transpired that he had been listless and easily tired for a month. His wife had noticed loss of weight and deterioration of memory. He had a slight cough.

On examination there was generalized muscular wasting with marked weakness and hypotonia of the lower limbs only. The biceps-jerks and left knee-jerk were present, all other tendon reflexes being lost. The plantar responses were extensor. There were cutaneous hypalgesia over the right hand, vibration sense was impaired below the costal margins and position sense was defective in the toes. There were signs of a left pleural effusion. No other abnormality was found. Blood pressure 140/90.

X-rays of the chest showed evidence of a left-sided carcinoma with disseminated carcinomatosis. Bronchoscopy was negative. His condition rapidly deteriorated with severe dyspnœa and altered consciousness. He was treated with 1,000 microgrammes of vitamin B_{12} intramuscularly daily without effect. He died on August 3, 1951.

Pathological Examination

Summary of necropsy (*P.M.* 294. 1951). *Collapse of lung. Pleural effusion. Lymphogenous secondary carcinoma of lungs. Primary carcinoma of left lung.*

Carcinoma (3 × 1·7 cm.) arising from a main bronchus to upper lobe at hilum. Collapse of lower lobe. Extensive growth forming sheets in parietal pleura of lower half of left chest. Secondary growth in a few lymph-glands at left hilum, and extensively involving anterior mediastinum. Secondary growth in right and left supraclavicular glands, gastro-coronary and cœliac glands. Numerous secondary deposits in liver, and three in marrow of upper shaft of right femur. Cortical adenoma (2 cm. diam.) in right suprarenal. No secondary growth in central

nervous system. Small vascular hamartoma (0·2 × 0·1 cm.) in lateral border of central white matter of right cerebellar hemisphere. Slight symmetrical dilatation of lateral ventricles. No visible degeneration or other change in spinal cord. A moderately wasted man.

Microscopical examination.—The growth in the left lung is an anaplastic, mainly oat-celled carcinoma. There are many scattered foci of secondary carcinoma in the thyroid gland, which shows elsewhere islands of adenomatous hyperplasia.

Central nervous system : In addition to the small vascular hamartoma in the cerebellum there is a diffuse, possibly agonal, degeneration of the granule-cell layer of the cortex. No further abnormality beyond post-mortem chromatolysis was found in the brain and spinal cord.

Posterior root ganglia : Those of cervical 8, thoracic 12 and lumbar 2 were examined and appear normal.

Peripheral nerves : Left ulnar, right radial, both phrenic, right sciatic, anterior and posterior tibial, and sural were examined. Endarteritis fibrosa with stenosis of an intrinsic artery in the anterior tibial and radial nerves has not produced any effect upon the nerve fibres, which appear normal. The other nerves are likewise normal.

Muscles : The levator palpebræ superioris, superior oblique and external rectus from the right orbit appear within normal limits for the age of the subject. The pectoralis major shows very slight atrophy of a few scattered fibres. In the left flexor sublimis, right soleus and the left abductor minimi digiti there is moderate atrophy of occasional scattered fibres with an increase in the number of sub-sarcolemmal nuclei. A minute focus of large mononuclear cells and small lymphocytes in the last-mentioned muscle surrounds a fibre that is apparently undergoing a more rapid degeneration. Cross-striation is in general excellent. In the diaphragm there is slight atrophy of a few fibres. Atrophy is more conspicuous in the right vastus externus, where the disparity in the calibre of the fibres is great. But there is no cellular infiltration nor fibrosis, and cross-striation is good. No abnormality of the intrinsic nerve-fibres and their terminations was demonstrated in Bielschowsky preparations.

Case 10.—*Male, aged* 59. *Admitted to The London Hospital, September* 22, 1951. (*L.H. No.* 36583/51.)

Four months previously he had developed aching pains in his calves, made worse by walking, loss of feeling in the feet and progressive weakness of the lower limbs. The pains disappeared in two weeks but the weakness increased and spread to his fingers and hands. There was loss of sensation in the fingers. He developed a productive cough and dyspnœa. One month before admission sensation returned to his extremities and the power in his legs improved, although at this time his pulmonary symptoms were growing rapidly worse.

Examination showed an ill, wasted man. There was weakness of dorsiflexion of both feet. The triceps-jerks were sluggish, all other tendon reflexes being lost. Vibration sense was impaired at the ankles and the calves were tender. No other abnormality was found in the nervous system. Blood pressure 170/90. There was clinical and radiological evidence of collapse of the whole left lung. The C.S.F. contained 55 mg. per cent protein and less than 1 cell per c.mm. Lange curve 111221. The W.R. was negative in blood and C.S.F.

Thoracotomy on September 26, 1951, showed an inoperable growth of the left lung. His general condition deteriorated rapidly with swinging pyrexia due to pulmonary suppuration. In spite of this his neurological condition improved without treatment. The absent tendon reflexes returned and he was able to walk

normally without assistance. He was discharged on November 7, 1951, and died at home on January 30, 1952. No post-mortem examination was made.

Case 11.—*Female, aged* 68. *Admitted to The London Hospital, November* 14, 1952. (*L.H. No.* 39979/52.)

This patient was admitted to Whipps Cross Hospital on November 6, 1951, complaining of weakness of the legs of rapid onset three months previously. Her thighs ached on walking and her feet felt dead. On examination she appeared well. There was generalized wasting and moderately severe weakness of hypotonic lower limbs. The arm-jerks were sluggish but equal. The knee and ankle jerks were absent. There were no other abnormalities in the nervous system or elsewhere. Blood pressure 175/95. X-rays of the chest, blood count, histamine test meal and blood and C.S.F. W.R.s were all negative. The C.S.F. contained 50 mg. per cent protein, but was otherwise normal. She was treated with 50 mg. vitamin E ("Ephynal") thrice daily. She began to improve in February 1952 and ceased attending shortly afterwards, stating later that her recovery had become complete. The knee and ankle jerks did not return.

On November 14, 1952, she was admitted to The London Hospital from Whipps Cross, complaining of headache, vertigo, diplopia and ataxia of three months' duration. Apart from signs of hydrocephalus and cerebellar dysfunction there was slight generalized weakness of the limbs and all her tendon reflexes were absent. The C.S.F. now contained 45 mg. per cent protein but was otherwise normal. Lange curve 012110. Chest X-ray was negative and an electromyogram was also normal. Pyruvate tolerance test: fasting blood pyruvate level 1·0 mg. per cent after 60 mins. 1·4 mg. per cent, after 90 mins. 1·6 mg. per cent. A diagnosis of carcinomatous neuropathy with cerebellar metastases was made. She died on March 16, 1953, still without clinical, radiological or bronchoscopic evidence of bronchial carcinoma.

Pathological Examination

Summary of necropsy (*P.M.* 111. 1953). *Heart failure. Secondary carcinoma of cerebellum. Primary carcinoma of bronchus.*

Ill-defined carcinoma (0·6 × 0·4 × 0·15 cm.) in mucosa of lateral apical bronchus in upper lobe of left lung, 0·8 cm. from origin. No secondary growth in rest of body apart from brain. Endocrine glands normal. Thymus replaced by adipose tissue. Expansion of right cerebellar lobe by two metastases. Great œdema of adjacent central white matter. No further growth in central nervous system. Conspicuous grooving of right medullary pyramid by atheromatous vertebral artery. Slight symmetrical dilatation of lateral ventricles. Considerable deformation of fourth ventricle and brain-stem by growth and œdema in cerebellum. Fibrous adhesion of arachnoid to dura mater over posterior aspect of third to fifth cervical segments, most marked on right side. Slight flattening of posterior columns in lower cervical segments. Poor demarcation between grey and white matter at all levels of spinal cord on transverse section. A slightly wasted woman.

Microscopical examination.—Lung: Oat-cell carcinoma in left upper lobe bronchus.

Brain: The right lobe of the cerebellum is occupied by secondary carcinoma composed of small polygonal and a few oat-cells. The surrounding white matter forms a zone of softening, containing many foam-cells. The left lobe of the cerebellum and the mid-brain appear normal. The fibres of the left trigeminal nerve, both within the pons and where they penetrate the pia, are in active stages of degeneration accompanied by congestion and an uneven infiltration by round

cells. The right nerve, however, is unaffected. In the upper medulla the latera half of the right pyramid and the olive are deformed by the vertebral artery. The deformed part of the pyramid is vacuolated and there is a diffuse partial loss of myelinated fibres. In other respects the medulla is unchanged.

Spinal cord : In the fourth, fifth and sixth cervical segments there is considerable demyelination and gliosis of the posterior columns which is maximal in an ill-defined central area in the upper two segments and forms symmetrical radial zones corresponding to the lateral borders of the column of Goll in C6. The degeneration is absent from all segments caudal to this. In the left lateral column their is a slight loss in the crossed pyramidal tract which fades out in the lower thoracic region. Again on the left there is slight loss at the margin of the lateral column in the position of the anterior spino-cerebellar tract, confined to C4, 5 and 6. In the last-mentioned segment a perforating vessel in the left lateral column adjacent to the grey matter is cuffed with small lymphocytes. The rest of the spinal cord and its roots appears otherwise normal.

Posterior root ganglia : In the left sixth cervical ganglion the attached posterior root shows a moderate loss of fibres and stages of Wallerian degeneration with occasional foci of small lymphocytes. The ganglion itself contains occasional residual nodules while the remaining neurones show a good deal of chromatolysis, and, occasionally, proliferation of capsular cells. Similar neuronal changes appear in the other ganglia examined (C4 right, Th12 right, L2 left and L4 right), but the attached roots are normal.

Peripheral nerves : The right median and sciatic nerves both show a slight diffuse loss of fibres but no definite evidence of active degeneration.

Muscles : Psoas appears normal. In the opponens pollicis severe atrophy affects groups of fibres. In these the nuclei form peripheral chains and, occasionally, central clumps. Elsewhere non-atrophied fibres are occasionally swollen and vacuolated. There is no cellular infiltration.

In the pectoralis major the muscle fibres in a few small areas show slight atrophy with an increase of connective-tissue between the fibres. Cross-striation is well preserved. A few lymphocytes are collected around one vessel.

In the diaphragm a few fibres are atrophied ; a fibre transversely cut has undergone vacuolar degeneration, and another, in longitudinal section, is occupied by a column of macrophages.

In Bielschowsky preparations of the psoas, opponens pollicis and pectoral muscles the preservation of the intrinsic nerve fibres and their terminations appears normal.

Comment.—The degeneration of the left crossed pyramidal tract is obviously due to the pressure by the vertebral artery upon the right pyramid. The other degenerative changes in the cervical cord are not reflected in the clinical picture, and their character suggests that they should be attributed to an extra-thecal lesion not detected at necropsy. The degeneration of the left trigeminal nerve may have been due to the gross deformation of the hind-brain by the cerebellar metastases.

Case 12.—*Male, aged* 38. *Admitted to The London Hospital, May* 2, 1940. (*L.H. No.* 30322.)

Four months previously he had noticed progressive weakness and severe cramp-like pains in the lower limbs. Examination showed slight generalized weakness of the lower limbs without wasting or fasciculation. The trunk muscles were also weak, and he had a dorsal kyphus of recent onset. The knee-jerks were present but the ankle-jerks were sluggish. The calves were tender. No other

abnormalities were found in the nervous system or elsewhere. The C.S.F. was completely normal. The W.R. was negative in the blood and C.S.F. A chest X-ray was normal.

He was readmitted on July 2, 1940 (L.H. No. 30498). The weakness of the lower limbs and trunk had progressed, and the shoulders, neck and arms were now involved. He also complained of aphonia, dysphagia, diplopia and lack of saliva. On examination there was moderate bilateral ptosis, but the pupils and external ocular movements were normal. The left vocal cord was partially paralysed and there was pharyngeal stasis. There was a severe atrophic paresis of the limb girdles and proximal parts of the limbs; power was only slightly reduced in the hands and feet. All trunk movements were weak. Although he complained that his head would fall forward owing to weakness of his neck, the neck movements were objectively normal. No fasciculation was seen. The arm and knee jerks were sluggish and the ankle-jerks were absent. The calves remained tender.

The subcutaneous injection of 1·5 mg. of neostigmine methylsulphate produced some subjective improvement in muscular power, particularly in the bulbar muscles; objectively this improvement was not convincing. Further injections and the administration of the drug by mouth were ineffective.

The bulbar symptoms and muscular weakness progressed rapidly for three weeks, the knee-jerks disappeared and the plantar responses became extensor. There was then a spontaneous, partial remission of weakness, affecting all muscle groups but most evident in the bulbar muscles. Treatment with vitamins B_1, B_2, D and E and injections of liver extract were started after this remission had begun. The remission lasted for one month. The weakness then began to grow steadily worse in all the affected parts. A left pleural effusion appeared a few days before death on August 28, 1940.

Pathological Examination

Summary of necropsy (*P.M.* 165. 1940). *Organizing bronchopneumonia. Carcinoma of bronchus.*

Firm white growth (10 × 6 cm.) in hilum of left lung, infiltrating lung and extending as a mass (about 9 cm. diam.) in mediastinum. Stenosis by growth of left bronchus and pulmonary artery. Invasion by growth of parietal pericardium about left pulmonary veins. Focal invasion of muscularis of œsophagus. No secondary carcinoma found in rest of body.

Back-pressure congestion of liver, spleen, kidneys and pancreas. Slight œdema of legs. No visible abnormality in brain, spinal cord, muscles and peripheral nerves. A well-developed, well-nourished man.

Microscopic examination.—Sections from the left lung show an anaplastic polygonal-celled carcinoma of the bronchus. Back-pressure congestion affects the liver, spleen and kidneys. No significant changes were found in the thyroid, pancreas, suprarenal or thymus.

Sections from the cervical and lumbar enlargements and a thoracic segment reveal no histological abnormality; the anterior horn cells are well preserved. A posterior root ganglion is included with the lumbar segment; it appears normal.

Three portions of peripheral nerve were taken for examination. Unfortunately, during the war, the information concerning their source was lost. From their calibre it is probable that two of them were tibial, the third either ulnar or median. There is no evidence of active demyelination in any.

Three portions of muscle, from the sternohyoid, vastus externus and right deltoid respectively provide considerable evidence of atrophy. In all three there are individual fibres, or groups of fibres, that are greatly diminished in size, their nuclei forming irregular clumps or chains at the periphery of the sarcoplasm.

There is no associated inflammatory reaction, no fibrosis and no loss of cross-striation. There are no acute degenerative changes in the muscle-fibres. The deltoid is least affected by the atrophy, which is greatest in the thigh muscle. Bielschowsky preparations of the sternohyoid and vastus externus show normal nerves and motor endings ; that of the deltoid muscle yielded no information.

Comment on pathology.—The histological investigation is inadequate. The evidence, so far as it goes, suggests a primary myopathy, but the atrophy observed is of a banal and unspecific type. The vastus externus muscle is valueless in this connexion owing to the great prevalence of atrophy of this type in any subject who has been confined to bed for several weeks or longer. The atrophy found in the sternohyoid muscle is regarded as significant, and likewise in the deltoid though the atrophy is least developed in this muscle.

Case 13.—*Male, aged* 44. *Admitted to The London Hospital, July* 17, 1946. (*L.H. No.* 30812.)

For eighteen months he had noted progressive weakness of the legs, chiefly proximally, with numbness and burning sensations in the thighs, hands and abdomen. Six months previously biopsy of enlarged glands in the neck was performed at another hospital, and this revealed the presence of secondary carcinoma. The lung was suggested as the site of the primary growth.

On examination there was diffuse wasting and weakness of the shoulder girdles and upper limbs. There was wasting of the lower limbs with weakness of hip flexion and to a lesser degree of extension and flexion of the knees. There was no weakness below the knees. The trunk muscles were weak. No fasciculation was seen. All tendon reflexes were lost except the left biceps and right triceps jerks which were sluggish. There was hypalgesia over the right forearm and hand and doubtfully over the lower part of trunk and anterior aspects of the thighs and legs. Postural sense was grossly impaired in the right fingers. In the cranial nerves there was fine nystagmus on lateral gaze, weakness of the right masseter and cutaneous sensory impairment over the distribution of the second and third divisions of the right trigeminal nerve. No other abnormalities were found in the nervous system. There were signs of collapse of the lower lobe of the right lung.

The C.S.F. contained 120 mg. per cent protein but was otherwise normal. Chest X-ray showed signs of collapse of the right lower lobe. He was treated with a course of deep X-rays to the cervical region, a diagnosis of secondary carcinomatosis of spinal roots having been made. The follow-up failed completely in this case, but he lived for several months after discharge.

Case 14.—*Male, aged* 60. *Admitted to The London Hospital, September* 30, 1946. (*L.H. No.* 31120.)

This patient was admitted for investigation of symptoms suggestive of peptic ulcer. On admission he also complained that for three months he had notice progressive weakness and wasting of the limbs, with tingling in his fingers and aching pains in all his limbs. On examination there was an atrophic paresis of the limb girdles and limbs, most evident proximally, without fasciculation. The knee-jerks were absent, all other tendon reflexes being present. There was no other abnormality in the nervous system. A chest X-ray was normal.

He was readmitted on November 10, 1946, as his weakness had progressed. Examination revealed increased weakness and wasting of the same distribution as before. The arm-jerks and left ankle-jerk were sluggish, both knee-jerks and the right ankle-jerk being absent. Both plantar responses were extensor. The C.S.F. was completely normal. The W.R. was negative in blood and C.S.F. Radiological examination of the chest and alimentary tract revealed no abnormality. He was

treated with weekly injections of liver extract and physiotherapy. His condition grew steadily worse.

He was admitted to another hospital with hæmoptysis on June 7, 1947. Apart from an increase in the degree and extent of his paralysis there was no alteration in the neurological state. An X-ray of the chest showed no abnormality. He died in status asthmaticus on June 11, 1947. Post-mortem revealed a small, centrally placed, oat-celled carcinoma of the lung. No macroscopic secondary deposits were found in the brain or elsewhere. The spinal cord was not removed.

Case 15.—*Male, aged* 53. *Admitted to The London Hospital, January* 1948 *and to Maida Vale Hospital, March* 8, 1948.

For one year he had noted progressive weakness of the lower limbs, mainly at the hips, and for three months weakness of the upper limbs. During the past two months he had developed weakness of the neck and jaw muscles, dysphagia, diplopia, bilateral ptosis and feebleness of his voice. All these symptoms were made worse by muscular exertion, his jaws becoming weak when he chewed meat and his eyelids drooping when he was tired or watched television.

Examination on March 8, 1948, revealed bilateral ptosis and facial weakness. There was no demonstrable weakness of the movements of the jaw or palate. His voice was rather slurred and flat, but phonation and swallowing appeared normal. There was slight generalized weakness of the limbs with a predominant affection of the flexors of the hips. The arm-jerks and ankle-jerks were sluggish, the knee-jerks being absent. The abdominal responses were absent. The plantar responses were flexor, though they had been extensor when he was examined in consultation on December 17, 1947. No other abnormality was found.

X-rays of the chest and a barium meal were negative. Injections of neostigmine, both subcutaneous and intra-arterial, had no effect on his muscular power. The C.S.F. was normal and the W.R. was negative in blood and C.S.F. The serum potassium was 18 mg. per cent.

He was treated with 15 mg. of neostigmine bromide thrice daily and 30 grains potassium chloride four times daily. His weakness varied considerably from day to day and from week to week. He felt that one period of considerable improvement was related to the potassium chloride, the increase in power often occurring about an hour after ingestion of the drug. By May 1948 his gait had become lordotic and waddling. There was a rapid increase in weakness after an operation for anal fissure in June 1948, but after a few days he again improved. He was not examined again, but it is known that he developed chest symptoms later in the year and was found to have a carcinoma of the lung. He died over two years after the onset of symptoms. There was no post-mortem examination.

Case 16.—*Male, aged* 55. *Admitted to The London Hospital, January* 16, 1950. (*L.H. No.* 3389/49.)

Nine months previously his legs had begun to weaken progressively. There was also numbness and aching in the lower limbs, mainly occurring on exertion. For three months he had noticed weakness and wasting of his left hand and vertical headaches.

On examination he was a wasted, ill-looking man. There was rotary nystagmus on lateral gaze and slight bilateral ptosis. There was a diffuse, atrophic paresis affecting the shoulder girdles and upper limbs, left more than right. The lower limbs were also weak the paresis being most marked at the hips. The trunk muscles were all weak. No fasciculation was seen. All tendon reflexes were lost. Apart from signs of emphysema no other abnormalities were discovered.

Radiological and bronchoscopic examinations revealed the presence of an

oat-celled carcinoma of the lung, and this was removed by left pneumonectomy on February 20, 1950. A muscle biopsy taken from the right calf showed no histological abnormality. The C.S.F. was completely normal; the W.R. was negative in blood and C.S.F. Carefully controlled injections of 2·5 mg. of neostigmine, made on two occasions before operation, produced no alteration in muscular power.

Before the operation the patient could walk only a few steps with support. Six weeks afterwards his hand-grip had improved and he was able to walk upstairs. Soon he was walking two miles without undue fatigue and at a normal pace. He was able to do a little painting, this being his occupation. Examination in June 1950 confirmed this striking improvement. His ptosis had disappeared and all tendon reflexes had returned, though they were sluggish. This remission lasted four months. Weakness then returned to his limbs and trunk and ptosis reappeared. The tendon reflexes diminished, the knee-jerks disappearing first. He was readmitted on August 19, 1950. A secondary deposit was found in the anterior abdominal wall. The C.S.F. was again normal. The blood pyruvate level was 1·0 mg. per cent and the serum potassium 19·4 mg. per cent. He was allowed home for a while, being readmitted to hospital in November and dying there on December 1, 1950. His weakness eventually became generalized and quite incapacitating, and signs of recurrence appeared in his chest and elsewhere. He was treated with 100 mg. of nicotinamide and 10 mg. aneurin thrice daily.

Pathological Examination

Summary of necropsy (*P.M.* 428. 1950). *Carcinomatosis. Old operation : Pneumonectomy for primary carcinoma of left lung.*

Secondary growth in left parietal pleura near apex of heart and under second rib. Secondary carcinoma in two lymph-nodes at hilum of right lung, lumbar glands, right suprarenal, body of pancreas and one in subcutis. Thymus replaced by adipose tissue. Considerable wasting of muscles. Secondary carcinoma (2 × 1·2 cm.) in subcortical white matter of left inferior frontal convolution, and (0·3 cm. diam.) in right half of pons at junction of tegmental and basal parts. No further visible abnormality in brain. Slight grey discoloration of anterior lumbar roots. Poor demarcation between grey and white matter throughout spinal cord. A well-built man.

Microscopical examination.—A small focus of secondary carcinoma occupies the pons as already described. The pons is otherwise normal, as is also the cerebellum. In the tegmental part of the medulla oblongata there is chromatolysis and shrinkage of scattered neurones in the motor nuclei of the vagus.

At some levels of the spinal cord the neurones of the anterior horns appear fewer than normal; stages of chromatolysis and shrinkage affect some of the surviving cells. These changes are in general variable, and are more evident in the lumbar cord than at higher levels. They are sometimes asymmetrical in the segment examined. Many neurones, however, are well preserved, though they contain large amounts of the acid-fast fuchsinophil granular material identified by Einarson (1953). In the twelfth thoracic segment there is perivascular cuffing with small lymphocytes of two vessels in the anterior horns, a similar focus in the left anterior root and two in the right posterior root. There is evidence of loss of myelin in the anterior roots. In frozen longitudinal sections through an anterior root of the cauda equina (fifth lumbar or first sacral), stained with Sudan III and Sudan Black, there is definite Wallerian degeneration and some associated round-cell infiltration.

Posterior root ganglia : Those of C6, C8, Th9, L1 and 4 were examined. The ganglia themselves are within normal limits. The attached roots in C8 and C4 contain a few ill-defined foci of large mononuclear and lymphocytic infiltration.

The anterior roots in C6, Th9 and L1 show uneven loss of myelin, with fibrosis and evidence of active Wallerian degeneration.

Peripheral nerves : The left ulnar, left median, left radial (forearm), left sciatic, left anterior tibial, left femoral and right phrenic nerves were examined. No changes were found except in the left anterior tibial where Wallerian degeneration involves a few fibres.

Muscles : The left pectoralis minor, left flexor sublimis, left abductor minimi digiti and left gastrocnemius muscles were examined. There is atrophy of individual fibres, separated by fibres of normal calibre, in all, but varying greatly in extent in the different specimens. The pectoral muscle is least affected. In general the affected muscle fibres are moderately reduced in calibre, and occasional fibres are grossly atrophied but without loss of cross-striation. In the flexor sublimis and abductor minimi digiti the diffuse atrophy is much greater, in occasional fibres extreme, and in the latter muscle these extremely atrophied fibres are sometimes embedded in fibrous tissue. Cross-striation is, however, preserved.

In the gastrocnemius fibres of normal calibre are mingled with grossly atrophied fibres (fig. 7). In places also there is acute degeneration, the fibres being greatly swollen, flocculent and vacuolated (fig. 8) ; in some there is infiltration of the sarcoplasm by leucocytes (fig. 9). No abnormality of the intrinsic nerve fibres and their endings was found in any of these muscles, using Bielschowsky's method.

Case 17.—*Male, aged* 56. *Admitted to The London Hospital, October* 6, 1952. (*L.H. No.* 34304/52.)

Two and a half years previously he had developed dryness of the mouth, aching pains and progressive weakness of the legs and a transient weakness of the arms which cleared in a few weeks. Eighteen months previously he had had to give up work because of the leg weakness. Examination in two other hospitals at that time showed considerable weakness of the muscles of the trunk and hips, with wasting and weakness of the quadriceps and hamstrings, more right than left. The knee and ankle jerks were absent. Vibration sense was impaired below the knees. He walked with a waddling gait. Many investigations, including muscle biopsy and X-rays of the chest, were negative. Test doses of neostigmine and quinine had no effect when first administered, but when an injection of neostigmine was given in the second hospital there was a remarkable improvement. He was able to walk almost normally. He was treated with 150 mg. of neostigmine bromide daily in view of this response. In three months he had recovered sufficiently to return to work, being left with a minimal residual weakness.

Two months before admission to The London Hospital he developed cough, dyspnœa and hæmoptysis. Examination revealed a gross kyphoscoliosis of long-standing. There was weakness of the abdominal and hip muscles and slight wasting and weakness of the quadriceps. The knee-jerks were present and the ankle-jerks absent. His gait was normal. Bronchoscopy and biopsy established the presence of an oat-celled carcinoma of the right main bronchus. The patient was discharged on October 25, 1952, as his growth was inoperable. He died at home in January 1953. There was no necropsy.

Case 18.—*Male, aged* 50. *Admitted to The London Hospital, June* 12, 1951. (*L.H. No.* 1316/50.)

This patient was first admitted on January 19, 1950, complaining of pulmonary symptoms of ten weeks' duration. He was found to have a neoplasm of the left lower lobe bronchus, and this was removed by lobectomy and lingulectomy. The growth proved to be an oat-celled carcinoma with secondary deposits in the bronchial lymph nodes. He remained well until January 1951 when he noticed

increasing weakness of the limbs following an attack of influenza. By June 1951 the weakness was disabling.

Examination showed a man with a dorsal kyphus and increased lumbar lordosis of recent onset. He walked with a waddling gait. There was a moderately severe atrophic paresis affecting the muscles of the shoulder girdles, and to a lesser degree the biceps and triceps, more left than right. The remainder of the upper limbs was normal. There was slight wasting of the glutei with weakness of all hip movements. Power was normal at the knees and ankles. The trunk muscles were all weak. The arm-jerks were all present and equal, the knee and ankle jerks being brisk and equal. Apart from a hypostatic eczema affecting the lower parts of the shins there were no other abnormalities.

The C.S.F. was normal. The W.R. was negative in blood and C.S.F. An electromyograph showed no evidence of denervation. The subcutaneous injection of 1·5 mg. neostigmine produced a temporary improvement in muscular power, more subjective than objective, which was almost equalled by a subsequent injection of sterile water.

He was treated with 100 mg. of *a*-tocopherol thrice daily by mouth. He also received aneurine and vitamin tablets and weekly injections of liver extract or vitamin B_{12}. His condition progressed slowly until October 1951 when it became arrested. This was two months after the initiation of treatment. At the height of his paralysis there was slight involvement of the muscles of the forearms and hands and moderate affection of the thighs. Power below the knees remained normal throughout. The arm-jerks were diminished or lost; the knee and ankle jerks remained active. Steady improvement began in May 1952 and has continued to date. The arm-jerks are now all present though sluggish. There has been a return of bulk and power to all affected muscles, and although the patient is still handicapped by weakness of limb girdles and trunk in particular he is able to work normal hours in his public house. There is no clinical or radiological evidence of recurrence of his growth. A recent electromyograph of the left supraspinatus showed fibrillation and high-frequency discharges suggesting neurogenic and myopathic lesions with changes at the end-plate.

Muscle biopsy (*June* 1951).—Samples of the affected supraspinatus muscle, with forearm muscle for control purposes were examined. Microscopically both are closely similar and are not obviously altered in any point of structure. Included bundles of nerve fibres also appear normal and in Bielschowsky preparations there is no obvious change in the motor nerve-endings in either muscle.

Case 19.—*Female, aged* 54. *Admitted to The London Hospital on June* 6, 1953. (*L.H. No.* 18079/53.)

Twelve months previously she began to have brief spells of diplopia about once a week. These persisted until her admission to hospital. For ten months she had noticed gradually increasing weakness of her legs. Seven months previously she had occasional nocturnal cramps in her calves for three weeks and later cramps appeared by day in both forearms when she gripped anything. Two months before admission she fell down twice because of the limb weakness. This was the summit of her paralysis which thereafter improved in a small degree. Direct questioning revealed that her left eyelid drooped occasionally and that she had had a cough for a fortnight, her sputum being occasionally flecked with blood.

On examination she was a moderately obese, healthy-looking woman. Her speech was slightly slurred. At rest a minimal ptosis, more evident left than right was visible; after exertion slight ptosis was clearly present. The cranial nerves and upper limbs were otherwise normal. The quadriceps were slightly wasted but no other wasting and no fasciculation were seen in the lower limbs. There was

moderate weakness of flexion of the hips and extension of the knees. Flexion of the trunk was also weak. Her weakness became more evident after walking a hundred yards. Both knee-jerks were absent. All other tendon reflexes were present and equal. There was no other abnormality in the nervous system. She had a left pleural effusion and slow auricular fibrillation. The blood pressure varied between 145/100 and 180/120. Apart from gross anxiety her mental state was normal.

The C.S.F. was normal and the W.R. was negative in blood and C.S.F. Bronchoscopy and biopsy revealed the presence of an inoperable spheroidal-celled carcinoma of the left lower lobe bronchus. Liver function tests were normal. Pyruvate tolerance tests were well within normal limits. The serum sodium was 300 mg. per cent and serum potassium 16·5 mg. per cent. The plasma and red blood cell cholinesterase readings (Michel's method) were as follows:

11.6.53:	R.B.C. 56	25.6.53:	R.B.C. 83	29.6.53:	R.B.C. 84
	Plasma 49		Plasma 39		Plasma 56

An electromyogram taken from both quadriceps muscles was completely normal. Muscle biopsy of the left quadriceps showed a few atrophic fibres, the subsarcolemmal nuclei forming strings and clumps. The intrinsic nerve-fibres were well preserved. There was no cellular infiltration. After a preliminary negative injection of saline she was given 2·5 mg. of neostigmine subcutaneously. A quarter of an hour later her walking capacity was more than trebled. The distance walked before injection was 125 yards with complete fatigue at that point. Afterwards she managed 400 yards with much less fatigue. This test was repeated on several occasions with careful measurement of the distances walked. There was never more than a slight variation in the results. The patient was therefore treated with 120 mg. of neostigmine by mouth daily with similar beneficial results. She was delighted with her improvement.

She was discharged on July 16, 1953. By then her diplopia had disappeared and her palpebral fissures were wider. She was speaking more rapidly and more clearly. Mentally she was now euphoric. After going home she rapidly became dyspnœic and died suddenly on August 10, 1953.

Pathological Examination

Summary of necropsy (*P.M.* 297. 1953). *Heart failure. Bronchopneumonia. Carcinoma of left lung.*

Massive carcinoma occupying greater part of left lower lobe, extending along main bronchus and into pericardial sac and left atrium. Secondary growth in hilar glands; no further secondary growth in body. Three small colloidal and cystic adenomata in thyroid. Remaining endocrine glands normal. Thymus replaced by adipose tissue. Chronic peptic ulcer in first part of duodenum. No visible abnormality in central nervous system, nor in spinal nerve-roots. Considerable post-mortem degeneration of tissues in general. A rather obese woman. (The patient died outside the hospital in hot weather and post-mortem examination was delayed for twenty-four hours.)

Microscopical examination.—Lung: Oat-cell carcinoma of bronchus. *Thymus:* Largely replaced by adipose tissue; a few islands of normal glandular tissue remain. *Suprarenal:* Infiltration of medulla by small lymphocytes, plasma cells and groups of small cells with oval nuclei, probably secondary carcinoma. *Thyroid:* Nodular foci of colloidal hyperplasia of varying size; degeneration of acini of residual glandular tissue; no fibrosis or cellular infiltration. *Pituitary:* Small chromophobe adenoma in centre of anterior lobe. *Heart:* Carcinomatous pericarditis; extensive carcinomatous infiltration of left auricle; no abnormality in muscle of right and left ventricles. *Central nervous system:* No abnormalities found in cerebrum, brain-stem, cerebellum and spinal cord beyond extensive

chromatolysis attributable to post-mortem degeneration. Spinal nerve-roots normal.

Posterior root ganglia : Four (from C3, C7, L3 and L4) were examined. Occasional residual nodules are present and there is considerable chromatolysis. *Muscles :* The right levator palpebræ superioris, complexus (neck), soft palate, œsophagus (upper and middle), diaphragm, abductor minimi digiti, psoas major and left quadriceps were examined. The muscle fibres of the soft palate, complexus and abductor minimi digiti appear normal. The pleural aspect of the diaphragm is infiltrated with secondary carcinoma and the atrophy of adjacent muscle fibres appears attributable to this.

Occasional fibres of the levator palpebræ superioris are atrophied, the subsarcolemmal nuclei forming strings. Vacuolation of the sarcoplasm affects one fibre. There are no lymphorrhages.

In the œsophagus there is considerable atrophy of the striped muscle fibres at the upper extremity, diminishing below this level ; in one area the atrophy is accompanied by fibrosis. There is no necrosis of fibres and no cellular infiltration. The unstriped musculature of the central œsophagus is unaltered. In the psoas a good many fibres are moderately atrophied, the subsarcolemmal nuclei occasionally forming short strings. Cross-striation is well preserved, as are the intrinsic nerve-fibres. In the left quadriceps the fibres are of very uneven calibre. The atrophy is similar to, but much greater than, that observed in the biopsy of this muscle. But apart from this there is no further change.

Discussion

Lennox and Prichard (1950) have shown that the association of polyneuritis and carcinoma of the lung is more than a chance one. Brain *et al.* (1951) state that "a review of the literature shows a high correlation of carcinoma with subacute cortical cerebellar degeneration." The significance of the association of carcinoma and neuropathy is even greater with sensory neuropathy and the group of neuromuscular disorders shortly to be discussed. Admittedly sensory neuropathy due to posterior root ganglion degeneration may occur in the absence of carcinoma as McAlpine and Page (1951) have suggested, but pathological confirmation is so far lacking. We have not encountered a clinical picture like that shown in Cases 12 to 19 in the absence of carcinoma of the lung nor are we aware of a previous description of the condition, although two of Lennox and Prichard's (1950) cases of polyneuritis are similar. Nevertheless we would not suggest that these neuromuscular disorders may not arise in association with other varieties of carcinoma, nor indeed that they may not be found in the absence of cancer.

The carcinomata in our patients were situated in the lung in 17 patients (3 females and 14 males) and in the breast and ovary in the remaining 2 (Cases 1 and 5). Both these latter patients had subacute cerebellar degeneration. Neurological symptoms preceded those directly due to the carcinoma or diagnosis of the growth in 15 of the 19 patients. The longest interval was twenty-eight months (Case 17) and in 6 other patients the period was more than one year. The presence of carcinoma was proved only at necropsy in three instances (Cases 11, 12, and 14).

Lung cancers were found at routine X-ray examinations, that is in the absence of pulmonary symptoms, in 4 patients (Cases 3, 9, 16 and 19). The ovarian carcinoma in Case 5 was felt vaginally with some difficulty. Secondary deposits in lymph nodes were the first manifestations of carcinoma in Cases 1 and 13. Altogether the diagnosis of carcinoma had not been made in 13 patients when we first saw them. Recognition of the clinical picture led to the discovery of the carcinoma in 10 of these. In the other 3 patients (Cases 12, 14 and 15), all of whom had bronchial carcinoma, chest X-rays were negative whilst they were under our care.

Clinical and Pathological Features

Cerebellar disorders.—The clinical aspects of subacute cerebellar or spino-cerebellar degeneration associated with carcinoma have been thoroughly described by Greenfield (1934) and Brain, Daniel and Greenfield (1951). The literature of the subject has been reviewed by Brain and his colleagues, and by Barraquer-Bordas and Lowenthal (1953). Less than 20 cases have been described with post-mortem examination. The carcinomata implicated have been situated in the ovary, lung, breast and uterus, those of the ovary and lung predominating. There are 5 examples of cerebellar disorder in our series (Cases 1 to 5). The carcinomata have been sited in the lung (3 cases) and in the breast and ovary (1 case each). 3 patients were examined post mortem.

All 5 patients have shown a mixed clinical picture. Vertigo was a prominent early symptom in Cases 1, 3 and 5 and in these 3 cerebellar ataxia was at some time the main disorder. Cerebellar symptoms were the dominating feature of the whole illness in Cases 3 and 5. In Case 1 gross signs of pyramidal lesions supervened after an early phase of cerebellar ataxia. Tremors of extrapyramidal type were conspicuous in Cases 1 and 5. It is noteworthy that, although Cases 1, 2 and 3 showed the euphoria and dementia which other workers have described, the fifth patient was in such a state of mental anguish induced by her physical state that pre-frontal leucotomy was necessary. Lack of data makes us unwilling to comment on the cause of the deafness in Patient 4, but the length of history makes it unlikely that secondary deposits were involved. Muscular wasting and weakness were evident in Cases 1, 2 and 4; indeed the predominant features of Case 2's illness were external ophthalmoplegia, bulbar palsy and weakness of the limbs. Sensory disturbances were prominent in Cases 2 and 4.

The clinical picture in these patients has therefore been variable and pleomorphic. The cerebellar symptomatology was of minor importance in Cases 2 and 4.

Histologically Case 5 alone shows a significant degeneration of the cerebellar cortex, and the central nervous system is affected at this level only. The other 2 cases (1 and 2) exhibit a combination of histopathological features for which the term "subacute cerebellar degenera-

tion" seems inappropriate. Thus the salient changes in Case 1 are degeneration and loss of motor neurones in the spinal cord and medulla oblongata : the picture is that of a chronic progressive poliomyelitis. Similar, though less advanced, changes were found in Case 2. A cerebellar element is, however, provided in Case 1 by the degeneration and loss of cells in the dentate nuclei coupled with a loss of fibres in the superior peduncles. Similar changes in the dentate nuclei are mentioned by Barraquer-Bordas and Lowenthal (Case 2), but here the inferior olives were similarly involved. They did not mention the subthalamic nuclei, which were selective and severely involved in our Case 1, and the spinal cord was not available for examination. But it is evident, comparing these cases with those described by Greenfield and Brain, Daniel and Greenfield, that the lesions in this "cerebellar" group include a variety that are both inconstant and not obviously referable to the cerebellum. Thus degeneration of the subthalamic nuclei, and of the pyramidal tracts and posterior columns of the cord, were noted by these authors. Cellular infiltration of the meninges and perivascular cuffing of the vessels of the spinal cord "not confined to the degenerated tracts but common in the grey horns," and in the medulla beneath the floor of the ventricle agree with our findings in Cases 1 and 2. The interpretation offered by Brain *et al.* for this infiltration, namely that it is reactive to degenerating nervous tissue does not agree with the absence of demonstrable local degeneration in many sites, and therefore requires an alternative explanation. A virus ætiology (discussed by Greenfield, 1934) seems more plausible especially as it is recognized that, quite apart from the virus theory of carcinogenesis, neoplasms sometimes harbour viruses as a secondary phenomenon (Cowdry, 1940).

The tremor noted clinically in Case 1 is explained by the degeneration of the subthalamic nuclei, but the latter is lacking in Case 5. The gross pyramidal signs found in Case 1 are unexplained histologically, though some degeneration of these tracts was observed in Case 2.

Significant cerebellar changes are lacking in the remaining cases of our series, since focal losses of the Purkinje cells are commonly found at necropsy in adults of middle age. Moreover, in agreement with Brain *et al.*, the diffuse granule-cell degeneration found in Case 9 is interpreted as an agonal or post-mortem change which has no bearing on our immediate problem.

Sensory disorders.—Denny-Brown (1948) has given a full account of the clinical and pathological findings in 2 patients who had sensory neuropathy in association with carcinoma of the lung. Dodgson and Hoffman (1953) described a similar condition arising in a patient with carcinoma of the œsophagus, but their pathological material was incomplete. In our series there are three further examples (Cases 6, 7 and 8) all occurring in association with carcinoma of the lung. 2 of the patients came to post-mortem examination. In these (Cases 7 and 8)

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the pathological changes agreed closely with those already described by Denny-Brown : degeneration and loss of the neurones in the posterior-root ganglia was accompanied by degeneration of the peripheral nerves and of the posterior columns. It is of interest that, in spite of the somewhat longer clinical course in Case 8, the degeneration appeared more advanced in Case 7.

Generally the clinical picture has closely resembled that described by Denny-Brown but there have been minor differences. First, pains in the limbs were severe in 2 of our patients (Cases 6 and 8) ; secondly, there have been signs of involvement of other parts of the nervous system, although the major manifestations have always been those of sensory neuropathy. Thus Case 7 had selective wasting and weakness of the intrinsic muscles of the hands and Case 8 had extensor plantar responses.

As we have already pointed out sensory disturbances have not been limited to patients with sensory neuropathy. 3 patients with cerebellar disorders had sensory symptoms or signs. Patient 2 was much afflicted by lancinating pains in the limbs and her calves were tender. Patient 4 had severe limb pains and troublesome paræsthesiæ with impairment of vibration and position sense in the lower limbs. Patients 9, 10 and 11 presented the clinical picture of polyneuritis, with paræsthesiæ in the hands and feet (Cases 10 and 11) and mild objective sensory disturbances, consisting of cutaneous sensory loss and impairment of vibration and position sense (Case 9) and loss of vibration sense and tenderness of the calves (Case 10). These sensory changes were mild compared with the loss of muscular power suffered by the patients. Sensory signs were rare in those patients whose illnesses were characterized by muscular wasting and weakness (Cases 12 to 19). Patient 13 had impairment of position sense in one hand and some cutaneous sensory loss. Patient 17 had impaired vibration sense at the ankles when examined at another hospital early in his illness. The only sensory sign we found in the 6 patients we examined personally was tenderness of the calves in Patient 12 who suffered intolerable lancinating pains in the limbs and severe muscular cramps. 2 patients (Cases 14 and 16) had paræsthesiæ mainly affecting the lower limbs and 1 patient (Case 19) had cramps alone. Other patients had mild muscular pains related only to the use of weak muscles.

Neuromuscular disorders.—Muscular wasting and weakness have been found in all save 4 patients (Cases 3, 5, 6 and 8). It must be emphasized that these changes were over and above any wasting due to malignant cachexia. In several patients the clinical picture was unusual as regards the distribution, character and course of the paralysis. Our clinical impression is that lesions probably occur at more than one level in the neuromuscular apparatus and that sometimes at least there is a disorder at the neuromuscular junction.

3 of the patients with cerebellar disorders had muscular wasting

(Cases 1, 2 and 4). In Cases 1 and 2 the wasting was generalized but in Case 4 the lower limbs only were affected. The distribution of the affection was consistent with a clinical diagnosis of polyneuritis but in Case 2 there was in addition external ophthalmoplegia and bulbar palsy of remittent type. Cases 9, 10 and 11 had rapid onset of limb weakness with sensory disturbances and loss of reflexes : clinically they were regarded as unremarkable cases of polyneuritis.

The group of cases 12 to 19 have presented an unusual problem and will be considered in some detail. The basic pattern of the clinical picture has been sufficiently constant to make their recognition a simple matter. All 8 patients suffered an atrophic paresis which was most marked in the limb girdles and proximal parts of the limbs ; indeed in 3 patients (Cases 17, 18 and 19) weakness was confined to these muscle groups at the initial examination and in 2 of them (Cases 17 and 19) there was no further extension of the paresis. In 3 other patients (Cases 12, 14 and 15) weakness elsewhere in the limbs was minimal at the outset. One patient (Case 19) had involvement of the lower limbs only throughout the whole course of her illness, though she also suffered from diplopia and ptosis. The lower limbs were affected first in 7 patients, in the other case all the limbs were simultaneously affected. Weakness of the trunk muscles was prominent in 5 patients, 4 of whom developed spinal deformities as a result of their weakness. The gait was lordotic and waddling in some instances, especially Cases 15 and 18. 2 patients complained of weakness of the neck muscles. No fasciculation was ever seen.

3 patients (Cases 12, 15 and 19) had ptosis and diplopia without pupillary abnormalities or overt defects of external ocular movements. Patients 12 and 15 had bulbar palsy, the features of which included weakness of the jaw, face and palate, dysarthria and dysphagia. Patient 2 also had ptosis and bulbar palsy with weakness of certain ocular movements ; in this instance the symptoms of bulbar palsy were the first manifestation of her neuropathy, and although the primary carcinoma was responsible for the final dysphagia and dysarthria in this patient there is little doubt that her earlier difficulties were neurogenic. We are satisfied that the difficulties of speech and swallowing (in Cases 12 and 15) were of nervous origin, but the dysarthria in Case 12 was partly due to involvement of the recurrent laryngeal nerve by tumour. Patient 16 is not included amongst those with ocular and bulbar symptoms as he had a small pontine secondary deposit.

The tendon reflexes were diminished or lost in the areas affected by weakness and sometimes beyond it, for example Case 17. In accordance with the distribution of the paralysis the knee-jerks have sometimes been lost first, in other cases the knee and ankle jerks have been lost simultaneously.

Apart from the various sensory disturbances, which have been

previously considered, signs of lesions elsewhere in the nervous system were limited to extensor plantar responses in 3 patients (Cases 12, 14 and 15), and although these were transient in Case 15 it is noteworthy that they were associated with loss of the superficial abdominal responses.

The history of muscular fatiguability given by Patients 15 and 19 may be reasonably termed myasthenic. Patient 2 had a similar complaint. Diagnoses of atypical myasthenia gravis had been made elsewhere in Patients 17 and 19, in both cases on the basis of a positive response to the injection of neostigmine. This diagnosis was also considered by us in Patient 12. In all cases, however, there were either signs of central lesions, sensory symptoms or, more particularly, early muscle atrophy with loss of tendon reflexes which made it clear that we were not dealing with the association of classical myasthenia gravis and carcinoma of the bronchus. The results of the injection of neostigmine have been conflicting. Carefully controlled experiments were negative in Cases 2, 15 and 16. The response was certainly positive in Case 19, and we are assured that this was also true in Case 17. The results in Cases 12 and 18 were equivocal; in Case 12 the response was largely subjective and was not maintained on repetition of the injections; in Case 18 there was certainly some improvement in muscular power after the injection of neostigmine but the response was almost equalled by the subsequent injection of sterile water. Unfortunately the problem was not pursued further in view of this latter finding.

The course of the complaint was remittent in 6 patients, in the other 2 (Cases 13 and 14) it was probably progressive throughout but our information is incomplete.

An analysis of the symptoms and signs in the 8 patients in this group shows that 6 had clinical evidence of lesions of the central nervous system or peripheral nerves or both, Cases 18 and 19 being the exceptions. In reaching this figure we have accounted paræsthesiæ and reduction or loss of tendon reflexes beyond the field of weakness as evidence of neural lesions. The clinical picture of Patient 18 suggested a myopathic lesion though electromyography eventually showed evidence of a combined lesion of nerve and muscle. Patient 19 presented myasthenic and myopathic features: her occasional muscular cramps were not regarded as evidence of a neural lesion. 2 of the patients with signs of nervous involvement (Cases 15 and 17) were generally similar—myasthenic and myopathic features predominating. The condition may therefore be described as one in which although there is generally evidence of neuropathy, either central or peripheral, there are frequently signs of myopathic or myasthenic disorders and these may occur alone. Clinical investigation points to the existence of lesions at more than one level in the neuromuscular apparatus.

Although necropsies were performed in 8 cases with clinical evidence of muscular wasting and weakness (Cases 1, 2, 7, 9, 11, 12, 16 and 19),

satisfactory pathological evidence of the responsible lesion was found only in Cases 1 and 2; more doubtfully in Case 16. In these there was degeneration and loss of the motor neurones of the spinal cord and brain-stem. There was no demonstrable degeneration of the peripheral nerves in Case 9, in spite of the clinical suggestion of polyneuritis. In the other example in this class (Case 11) there was a slight loss of fibres in the peripheral nerves, without evidence of active degeneration. Clinical recovery in respect of the "polyneuritis" had, however, been in progress at the time of death.

Again the significance of such histological changes as were noted in the muscles in these cases is doubtful. Thus, in Case 18, biopsies were at the same time taken from an affected muscle (supraspinatus), and from an unaffected muscle (forearm) for comparison. Microscopically both appeared normal. In the other cases listed a variable degree of atrophy of the muscle-fibres was noted in certain muscles in all. In general this change was slight and of an unspecific character, the only obvious structural changes being a reduction of diameter, and the formation of chains of subsarcolemmal nuclei. The affected fibres were usually scattered amongst those of normal size, but occasionally they formed small groups. Greater significance may be attached to such findings in muscles of the orbit (Case 19), neck and forearm (Cases 9, 11, 12 and 16), diaphragm (Cases 9 and 11), and upper alimentary tract (Case 19) since these muscles are more exercised in patients confined to bed than those of the lower limbs and trunk. On the other hand it is noteworthy that in Case 5, exempted clinically from this class, the atrophy was considerably greater in a small muscle of the hand and the sternomastoid than in any other case examined.

The muscles of the leg are obviously unsatisfactory in the assessment of atrophy in the bedridden patient. In any wasted subject, whether carcinomatous or undernourished, the atrophy of muscles of the lower limbs appears greater than elsewhere (fig. 10). The vastus externus seems to be particularly affected, but we have not compared this muscle with others of the thigh in individual cases. Gross carcinomatosis with cachexia was not a feature in any of our cases.

Necrosis of individual fibres was noted in Cases 8, 9, 11, 16 and 19. This resembled the change described by Denny-Brown in the calf muscles in his two cases. The gastrocnemius was severely affected (figs. 8, 9) in Case 16 of our series, and slightly in Case 8; no other muscle was similarly affected in these. Again we question the importance of this change in relation to our present problem. A somewhat similar necrosis of individual fibres occurs in myasthenia gravis (Russell, 1953), in rheumatoid arthritis, and may also be found in gross malnutrition (figs. 11, 12).

We therefore consider that such muscle-changes as were found lack specificity. Moreover they are disproportionately slight in relation to the

observed clinical disability. In Cases 2, 12 and 19 there was some clinical resemblance to myasthenia gravis; but the histology in general, both of the muscles and of the thymus (though this is inconstantly affected in myasthenia gravis), is against this diagnosis. There is certainly no histological resemblance to dermatomyositis.

Miscellaneous.—Pyramidal signs were found in 10 patients but they were only remarkable in Patient 1 who had the most intense spasticity and active tendon reflexes we have ever seen. Otherwise the findings were usually limited to extensor plantar responses, although ankle clonus and loss of the superficial abdominal responses were also recorded. Pyramidal signs were found in all patients with cerebellar disorders, in 3 with the unusual neuromuscular disorder we have just described and in one each with sensory neuropathy and polyneuritis. Extrapyramidal disturbances were limited to the coarse irregular tremors noted in Patients 1 and 5. The mental changes occurring with cerebellar disorder have already been mentioned. Dementia was an early feature of the illness of Case 9 whose main disability was apparently polyneuritic.

It will be seen from the clinical histories and the analysis of the findings that although pure forms of the various types of neuropathy do occur there are intermediate linking cases and many patients showed a mixed picture. Thus Patient 6 had a pure sensory neuropathy and Patient 18 an entirely neuromuscular disorder. On the other hand there were patients with these conditions who had clear evidence of lesions elsewhere in the nervous system. It is in the group with cerebellar disorders that the most pleomorphic picture is seen.

Investigations

The investigation of these patients has not been an easy matter. The remittent course of the condition and the need for treatment of the underlying carcinoma have proved complicating factors. Some patients have been too ill with pulmonary symptoms to allow detailed laboratory or electro-physiological investigations. For these reasons some of the cases have been less fully explored than we would have wished.

Only 2 of our patients with cerebellar disorders (Cases 1 and 5) showed the characteristic cerebrospinal fluid changes described by Greenfield (1934) and Brain *et al.* (1951). In both these patients the fluid returned to normal in a few weeks from the first examination. The fluid in Patient 2 was mildly abnormal, the protein content being 45 mg. per cent and the Lange curve 222110, but in the others it was quite normal. Amongst the other patients there were slight increases in the protein content in Cases 6, 10 and 11 and a considerable elevation in Case 8. There were minor alterations in the Lange curve in Cases 6, 10 and 11. These patients had either sensory neuropathy (Cases 6 and 8) or polyneuritis (Cases 10 and 11). The fluid returned to normal whilst Cases 6 and 8 were under observation. The raised protein content in Case 7 was discounted by the presence of

intracranial metastases. Patient 13 had 120 mg. per cent protein in his spinal fluid but he alone in this series was inadequately followed and the co-existence of secondary deposits cannot be entirely excluded. It is noteworthy that the C.S.F. was completely normal in the other 7 patients with neuromuscular disorders. The W.R. was negative in the blood and C.S.F. in every case.

Blood counts have shown no abnormality beyond secondary anæmia and polymorphonuclear leucocytosis attributable to the primary growth and pulmonary suppuration. Fractional test meals have not revealed any abnormality. Estimations of the serum potassium have fallen within the normal range in the 3 patients in whom they were performed. The pyruvate tolerance test was abnormal in Patient 11 although it was performed at a time when the neuropathy had remitted. Heathfield (1952) and Kremer and Pratt (1952) reported similar findings in patients with polyneuritis and sensory neuropathy respectively associated with carcinoma. The test was negative in Patient 19 and an isolated reading of the blood pyruvate was normal in Patient 16. Estimations of the plasma and red blood cell cholinesterase were made by Michel's method in Patients 5 and 19 : no significant abnormality was found. We are neglecting the isolated low reading for plasma cholinesterase in Patient 19.

Electromyograms have been performed in Patients 5, 18 and 19. The records in Patient 5 and 19 were completely normal. Two recordings made in Patient 18, at a time when his condition was progressing, showed no specific changes ; in view of the clinical picture and the absence of electro-physiological evidence of denervation this finding was interpreted as favouring a myopathic condition. Later examinations, made two years after his remission had started, showed evidence of a compound lesion.

The Course of Carcinomatous Neuropathy, Including Its Relationship to the Underlying Carcinoma

We have already discussed the question of time of onset of neurological symptoms and diagnosis of the carcinoma, either because local symptoms had appeared or investigations had revealed the presence of growth.

Death has been directly due to the underlying carcinoma in 16 of the 18 patients who have died. The only exceptions were Patients 1 and 5 who had cerebellar disorders associated with carcinoma of the breast and ovary respectively. In both these cases the neurological state was the prime cause of death, necropsy revealing only local glandular secondary deposits in Case 1 and in Case 5 insufficient visceral involvement by growth to lead to death. All the other patients had carcinoma of the lung, death being generally due to the primary growth. Intracranial metastases were responsible for death in Cases 7 and 11. The neurological condition was often an important contributory factor, especially when there was advanced weakness or bulbar palsy. In view

of these facts a detailed consideration of the duration of the neuropathies is of little value. Nevertheless many patients survived long enough to enable us to study the pattern of the neurological disorder. We would draw attention to the fact that all our patients with cerebellar disorders lived for more than one year and 2 who received early surgical treatment for their lung cancers (Cases 3 and 4) survived for two years (cf. Brain *et al.*, 1951). Four patients with neuromuscular disorders lived for two years or more and 1 patient (Case 18) is alive and well three years after the onset of symptoms and four years after the removal of his carcinoma.

Fourteen patients survived long enough and were followed sufficiently thoroughly to allow a study of the course of their neurological illness and of its relationship in time to that of the carcinoma (Cases 7, 8, 9, 13 and 14 are excluded). Arrest or remission of the neuropathy has been a common finding. Where the main disability has been cerebellar disorder, arrest only has been seen. In Cases 1 and 3 the condition ceased to progress twelve and six months after onset respectively. Patient 3 grew steadily worse for a period of six months by which time he was virtually decerebellate. Spontaneous arrest then occurred and there was no significant alteration in his neurological state during the remaining eighteen months of life ; he died from recurrence of his carcinoma. Earlier the removal of his bronchial cancer had had no effect on the neuropathy. Remissions occurred in Patients 2 and 4 but these were at times when the symptoms were ophthalmoplegia and bulbar palsy (Case 2) and sensory disturbances (Case 4). The remissions in Case 2 were spontaneous whilst that in Case 4 followed pneumonectomy. In Case 5 the disorder ran a steadily progressive course.

We were able to follow the course of sensory neuropathy in one patient only (Case 6). The neuropathy had apparently reached its height by the time of admission, that is, four months after onset. There was no significant change in the neurological condition during a further fourteen months' observation. The arrest of the neuropathy was spontaneous. Pneumonectomy did not lead to any objective improvement, although his general condition was vastly bettered and his limb pains disappeared.

Remissions have been a feature in the patients suffering in the main from polyneuritis or neuromuscular disorders ; all 9 of these patients who have been adequately observed have had partial or complete remissions. Nevertheless, as we have already stated, we have some reason to believe that the neuromuscular disorders may run a steadily progressive course. Complete subjective recoveries were seen in Patients 10 and 11. Patient 10 recovered spontaneously from his polyneuritis at a time when he was desperately ill from a large bronchial carcinoma with associated pulmonary suppuration. Patient 11 made a complete subjective recovery from her polyneuritis over a period of some six months

though her tendon reflexes never returned. She had been treated with vitamin E for three months before recovery began. There was no recurrence of symptoms during the remaining year of life.

The remissions in patients with neuromuscular disorders were less complete but in some cases no less striking. Patient 12 had a spontaneous remission lasting one month only. Patient 15 had frequent periods of improvement which usually lasted a few days at a time. He believed they were associated with the administration of potassium chloride, but this alleged connexion does not bear scrutiny in view of the normality of the serum potassium and of the time relationships of the ingestion of the drug and the spells of increased muscular power. More significant and lasting improvement was seen in Patients 16, 17, 18 and 19. None of these patients had clinical evidence of central lesions. Patient 16 showed a dramatic temporary recovery after pneumonectomy as recounted in the history, relapsing four months later. Patient 17 began to improve about a year after the onset of symptoms, the change for the better being apparently related to treatment with neostigmine. His muscular power returned almost to normal and was unaffected during the last few months of life by the rapid progression of his bronchial neoplasm. Patient 18, who developed his paralysis eleven months after the excision of his carcinoma, experienced arrest of his symptoms nine months after onset, certain improvement only becoming manifest some nine months later. He has continued to improve over a further period of eighteen months. He was treated with various vitamins, especially vitamin E; arrest occurred two months after treatment began but improvement was deferred for a further nine months. Patient 19 had a spontaneous remission which had already begun when she came under observation. The rapid growth of her carcinoma led to early death, but there was no doubt of the improvement in her muscular power and her diplopia disappeared. Treatment with neostigmine appeared to contribute to her later improvement.

Lennox and Prichard (1950) noted that one of their patients had a spontaneous remission. The arrest in our Patients 3 and 6 and the remissions or recoveries in Patients 2, 10, 12, 15 and 19 were clearly spontaneous. We doubt whether the administration of vitamin E in Patients 11 and 18 can be credited with the ensuing improvement in view of the time interval between the initiation of treatment and the onset of recovery. Similarly we do not consider that neostigmine was responsible for the recovery of Patient 17 although it was of value in treatment both here and in Patient 19. Remissions in Patients 4 and 16 were apparently related to surgical removal of their growths, but in view of our observations on the lack of parallelism in the courses of the neuropathies and the associated carcinomata we doubt whether there was any causal relationship between the two events. Carcinomatous neuropathy is clearly a condition in which there is a marked tendency

— to spontaneous remission and this makes the assessment of treatment extremely difficult.

In 10 cases the clinical courses of the neuropathy and carcinoma were clearly divorced. Patients 3, 6, 10, 11, 17 and 19 are all good examples of this dichotomy, but Patient 18 was the most remarkable, for his neuropathy, or myopathy, developed eleven months after the removal of his carcinoma. As the clinical histories show, small or undetectable growths were accompanied or even perhaps preceded by profound neurological disorders which became arrested or regressed as the carcinoma enlarged; alternatively a neuropathy developing shortly before a large carcinoma became manifest might abate in the face of rapid progression of the tumour, e.g. Case 10. On the other hand the courses of the cancer and neuropathy were roughly parallel in 4 patients (Cases 1, 4, 5 and 16). The carcinoma in Case 1 was very small and could not be detected by palpation of the breast when the carcinomatous glands in the axilla were removed early in the illness; the ovarian carcinoma in Case 5 must also have been extremely small when the neuropathy began twelve months before any mass could be felt vaginally. In 2 patients (Cases 4 and 16) the correlation was more striking, both patients having remissions after the excision of their growths, but as we have previously said we doubt whether this apparent relationship was really significant.

Differential Diagnosis

The diagnosis of carcinomatous neuropathy embraces such a wide field that only the neuromuscular disorders will be considered in any detail. The clinical differentiation of the cerebellar form from disseminated sclerosis is not usually difficult though this was a real problem at the first examination of Patient 3. Subacute cerebellar degeneration and polyneuritis may, of course, occur in the absence of carcinoma and, as we have already remarked, the same may be true of the other manifestations of carcinomatous neuropathy described. However, we would stress the fact that many months and even years may elapse before the underlying carcinoma can be detected. Ironside (1953) had a patient with sensory neuropathy whose bronchial carcinoma could not be found until three and a half years after the onset of neurological symptoms. This is the longest intervening period of which we have knowledge.

In discussing the diagnosis of the neuromuscular disorders we will also consider the possibility that here we were dealing with the coincidental occurrence of some other recognized neurological disorder, that is apart from the question of probabilities which we have already discussed. It is submitted that reasonable clinical and pathological evidence has been produced to show that secondary deposits were not responsible. Other conditions which have had to be considered in diagnosis include myasthenia gravis, motor neurone disease, dermatomyositis, myopathy of late onset and chronic thyrotoxic myopathy. We have already com-

mented on the clinical features which distinguish this complaint from myasthenia gravis. Further the changes in muscles differ from those collectively described in myasthenia gravis (Russell, 1953). Some of our patients have been diagnosed as suffering from motor neurone disease, but there are obvious differences in the clinical picture, particularly the course of the disease and the entire absence of fasciculation. It is interesting to note that Lawyer and Netzky (1953) recorded only one instance of the association of carcinoma and motor neurone disease in 46 patients with this neurological disorder examined post mortem. Dermatomyositis may present with bulbar palsy, muscular wasting and spontaneous muscular pains (Matthews and Burne, 1953), thus resembling the syndrome under review. However, the constant absence of skin lesions and supporting pathological evidence excludes this condition which has been described in association with carcinoma of the lung (McCombs and MacMahon, 1947, and others). Chronic thyrotoxic myopathy is excluded by the complete absence of signs of thyroid intoxication (Millikan and Haines, 1953) and by histological examination of the thyroid which was significantly altered only in Cases 1 and 2. The recognized myopathies of late onset are differentiated by the course of the disease, signs of peripheral and central nervous lesions and sensory disturbances. Separation from this group of muscular disorders may be clinically difficult in the early stages, indeed we are concerned here with a condition in which muscle is primarily affected.

Nosology

It is clear that in this problem of carcinomatous neuropathy we are dealing with a loose linkage of various clinical syndromes in which lesions may occur at almost any level in the nervous system and also in muscle. Although subacute cortical cerebellar degeneration and sensory neuropathy associated with carcinoma constitute well-defined clinico-pathological states we do not suggest that carcinomatous neuropathy as a whole forms a nosological entity. We can only affirm that this wide range of unusual neurological disorders accompanies carcinoma with a significant frequency.

Ætiology

These neuropathies are undoubtedly rare and it is certain that more than one factor must be concerned in their production. Investigations of age, sex, family history, occupation and nutritional state have revealed no answer to the question why some patients with carcinoma are affected and others spared. Further, although bronchial cancer is the associated growth in the great majority of patients it is important to recall that carcinoma of breast, ovary and uterus may accompany similar or identical neuropathies, the group of so-called subacute cerebellar degenerations. However, the linking factor or factors between carcinoma

and neuropathy may operate in similar ways despite the varying sites of the growths.

In view of our observations on the relative courses of carcinoma and neuropathy we find it difficult to believe that there can be any direct causal relationship between the one and the other; we would rather suggest that they are linked by a common cause. The search for the causes of carcinomatous neuropathy is more concerned with carcinogenesis than with carcinoma. We cannot subscribe to the suggestion of Barraquer-Bordas and Lowenthal (1953) that the condition is carcinotoxic. It is emphasized that the various muscle atrophies we have described were not manifestations of general malnutrition or cachexia; this will be apparent from a study of the case reports.

The question of a virus ætiology has already been mentioned in regard to Patients 1 and 2. A virus infection certainly seems the most plausible interpretation of the pathological findings. Nevertheless changes of this sort were limited to 2 patients and it must be confessed that we have no evidence leading us to inculpate a virus in the other cases.

Denny-Brown (1948) suggested that sensory neuropathy might be a form of nutritional neuropathy and mentioned metabolic disorders of vitamin E or pantothenic acid as the possible basis of the disorder. In view of the need to postulate disturbances which may operate at so many levels this is an attractive hypothesis. It is interesting to note that myasthenic syndromes may occur as a manifestation of nutritional disorders of the nervous system (Denny-Brown, 1947). We have noted the abnormalities in the pyruvate tolerance test which have been recorded and which we have found in one patient. This is a point which needs further study.

We have considered the possibility that vitamin E may be involved. In experiments with adult rats Einarson and Ringsted (1938) found that certain neuromuscular lesions followed vitamin-E deficiency. There are many points of resemblance between this experimental condition and the human condition now surveyed. Einarson (1953) has summarized this work and described the additional feature of fluorescent, acid-fast deposits in the neurones of the central nervous system and elsewhere in the vitamin-deficient rats. Controls were negative in this respect. In human material, as noted by Einarson (loc, cit.) such deposits are found "more or less mixed with the usual lipochrome substances." We submitted sections of the spinal cord in Cases 1, 2, 7, 8, 9 and 16, with controls from males aged 15 and 43 respectively, to Einarson for examination. He kindly reported a trace in the younger control; a small amount of deposit in the older control, while the remainder showed greater amounts which were maximal in Cases 8, 9 and 16.

The significance of these acid-fast deposits in human subjects is obviously more difficult to assess than in the rat. Age may well be a

factor since in Case 7 the subject was 35 years old, and all those with greater amounts (Cases 1, 3, 8, 9 and 16) ranged in age from 56 to 64.

Our material does not suggest that disorders of the thyroid or thymus are concerned, though Patient 1 had treated myxœdema and the thyroid in Patient 2 showed atrophy and fibrosis on pathological examination.

Investigation of the plasma and red blood cell cholinesterase was prompted by the fact that Hunter's cases of "Mipafox" poisoning (Bidstrup, Bonnell and Beckett, 1953) showed signs of lesions at various levels in the neuromuscular apparatus and also, in 1 patient, in the pyramidal system. "Mipafox," a new organic phosphorus compound, is an inhibitor of cholinesterase. The tempo and distribution of the paralysis were very different from that seen in our patients but the analogy seemed close enough to warrant exploration. The idea was also attractive as a biochemical disorder of this sort might explain the occurrence of nervous and muscular disorders in the absence of lesions detectable by the usual histopathological methods; for instance disturbances of this kind at the myo-neural junctions, or at the synapses, might be responsible. Our findings were negative but as they were incomplete further observations on this point are required.

Treatment

This is obviously directed to the underlying carcinoma. The difficulty of assessing the results of treatment have already been mentioned. Where myasthenic symptoms are present or where neostigmine alleviates the muscular weakness it is clearly reasonable to give the drug for as long as may be necessary. We doubt whether vitamin therapy has been of any value in our patients but we feel that in our present state of knowledge adequate doses of vitamins, especially B_1 and E, should be provided.

Conclusion

We realize that in publishing our findings we are raising more questions than we answer. We are particularly dissatisfied with our failure fully to account for the gross muscular wasting and weakness which was so evident in many of our patients. It appears to us that biochemical and histochemical studies offer the most promising lines for further research into these difficult problems : more detailed and serial electromyographic examinations are also required.

Summary

19 cases of carcinomatous neuropathy and myopathy are reported. In 17 of the patients the underlying carcinoma was situated in the bronchus. The diverse clinical and pathological findings are described and discussed.

We are grateful to Sir Russell Brain who stimulated our interest in these problems and allowed us full access to his patients. We also acknow-

ledge the courtesy of our other colleagues who permitted us to include their patients in this report, and of Professor Lárus Einarson for his demonstration of acid-fast granules in a selection of our preparations.

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PLATE I

LEGENDS FOR FIGURES 1—6

FIG. 1 (*Case* 1).—Anterior horn of second lumbar segment to show loss of neurones (three seen below at periphery of horn); perivascular cuffing, and a cluster of small round cells marking site of neuronophagia. Hæmatoxylin and eosin. × 49.

FIG. 2 (*Case* 1).—Eighth cervical segment showing degeneration of ventro-lateral columns. Loyez' hæmatoxylin. × 5.

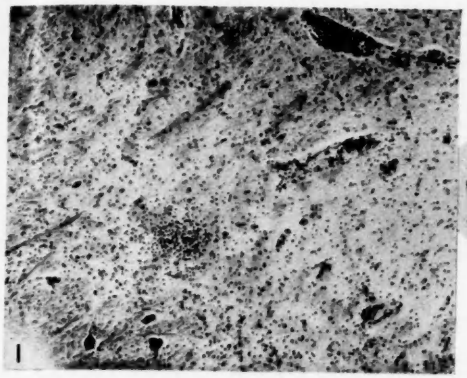
FIG. 3 (*Case* 2).—Border of anterior horn in sixth cervical segment. Cuffing of an arteriole in adjacent white matter and a small focus (top left) of cellular infiltration indicating neuronophagia. Hæmatoxylin and eosin. × 67.

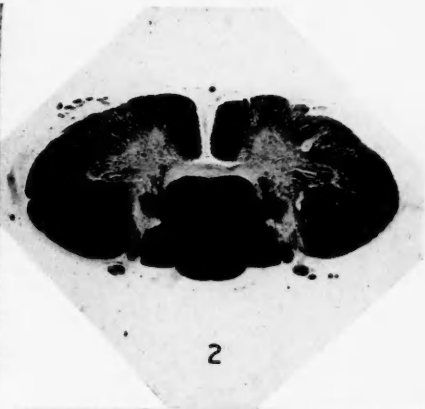
FIG. 4 (*Case* 2).—Sixth cervical anterior root showing uneven loss of fibres (myelin sheaths appear black). Phosphotungstic-acid hæmatoxylin. × 57.

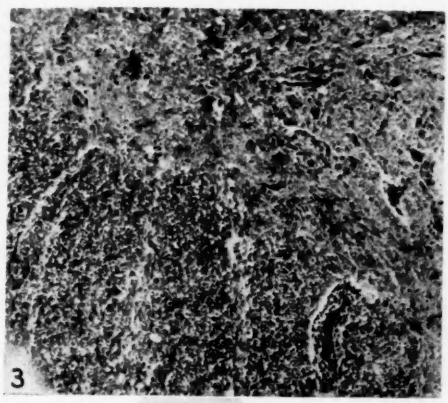
FIG. 5 (*Case* 7).—Degeneration of posterior columns in second thoracic segment. Loyez' hæmatoxylin. × 6.

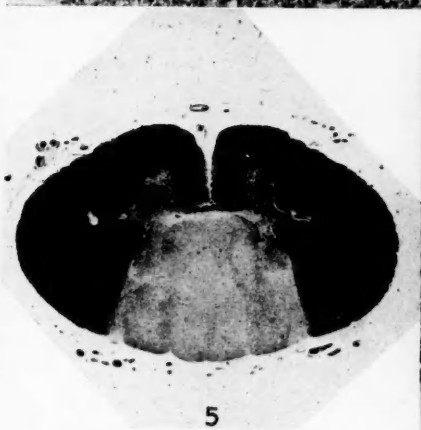
FIG. 6 (*Case* 7).—Fourth lumbar posterior root ganglion to show scanty neurones and numerous residual rosettes. Hæmatoxylin and eosin. × 66.

PLATE I



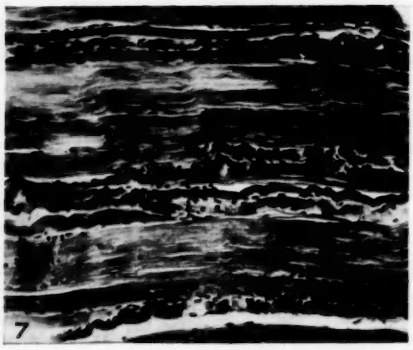


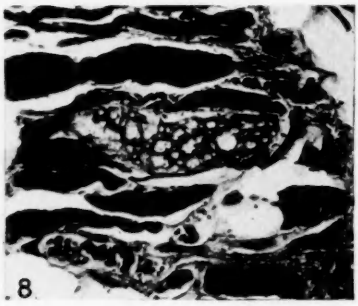


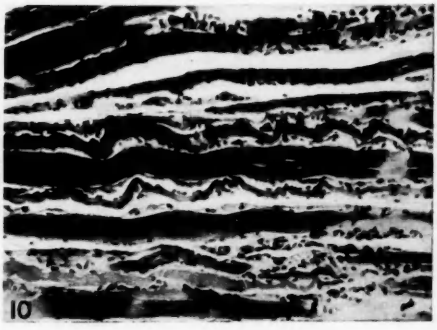


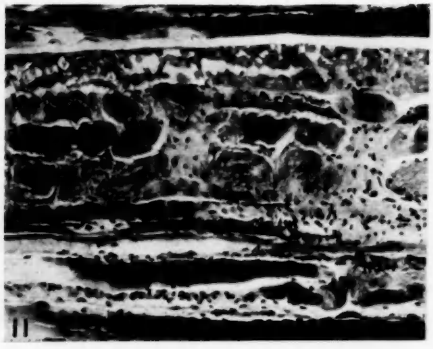
To illustrate article by R. A. Henson, Dorothy S. Russell and Marcia Wilkinson.

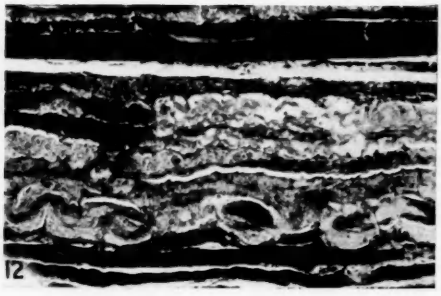
PLATE II











To illustrate article by R. A. Henson, Dorothy S. Russell and Marcia Wilkinson.

PLATE II

LEGENDS FOR FIGURES 7—12

FIG. 7 (*Case* 16).—Gastrocnemius muscle to show gross atrophy of scattered fibres. Hæmatoxylin and eosin. × 105.

FIG. 8.—Same as in fig. 7, showing acute vacuolar degeneration of a fibre. Phosphotungstic-acid hæmatoxylin. × 105.

FIG. 9.—Same as in figs. 7 and 8 to show invasion of a necrotic fibre by leucocytes. Phosphotungstic-acid hæmatoxylin. × 105.

FIG. 10.—Vastus externus from a man aged 74 with gastro-jejuno-colic fistula to show gross atrophy of fibres. Hæmatoxylin and eosin. × 103.

FIG. 11.—Same as in fig. 10 to show necrosis and vacuolation of fibres (compare with fig. 8). Phosphotungstic-acid hæmatoxylin. × 107.

FIG. 12.—As in fig. 11. Fragmentation of myofibrils is seen near lower border of field. Same stain. × 105.

PERIPHERAL NEUROPATHY AND MYOPATHY ASSOCIATED WITH BRONCHOGENIC CARCINOMA

BY

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ALTHOUGH earlier authors (Oppenheim, 1911) had reported the occurrence of peripheral neuritis in malignant disease, a definite association between peripheral neuropathy and carcinoma of the bronchus was not established until Denny-Brown published his two cases in 1948. One of his cases had been shown by Kendall at the Royal Society of Medicine in 1939 as an obscure case of sensory neuropathy, and Parkes Weber and Hill (1933) had even earlier reported a case of "chronic degeneration of the posterior columns with chronic polyneuritis in a case of widespread carcinomatous disease," the primary neoplasm being in the lung. Denny-Brown showed that the primary lesion in the peripheral nervous system was a chronic degenerative process of the cells of the posterior root ganglia with secondary degeneration of the posterior nerve roots and the sensory fibres in the peripheral nerves. Wallerian degeneration was present in the posterior columns and the skeletal muscles showed pathological features that he termed a chronic myositis, with only slight changes in the motor nerve fibres.

Lennox and Prichard (1950) reported on the incidence of peripheral neuritis with bronchial carcinoma at Hammersmith Hospital where numerous cases of malignant disease were sent for deep X-ray therapy; amongst the histories of 299 cases of bronchial carcinoma they found 5 presenting with peripheral neuropathy, 2 of these they had examined personally and pathological material was available, to some extent, in 3. The neuropathy was a mixed one, with maximal involvement of the motor nerves, none of the findings described by Denny-Brown was present. It seemed, therefore, that even within the syndrome there might be variations and that a mixed type of peripheral neuritis was commoner than a purely sensory one, and Elkington (1952) has observed 3 such cases in the past four years.

Bronchial carcinoma may also be associated with muscular disorders and the clinical picture may resemble myasthenia gravis or myopathy of late onset.

In the past two years we have observed 4 cases of this association, 1 of which (Case 3) has been reported previously (Heathfield, 1952). In 2 cases, both of which resemble Denny-Brown's closely, post-mortem material was available, in the third no post-mortem was done and the last patient is still alive.

Since the paper was begun a fifth case has been seen with myotonia as the most striking feature of a mild mainly sensory neuropathy.

Case 1.—A dock labourer, aged 62, was first admitted to Bethnal Green Hospital on January 11, 1949. Three months before admission he had an influenzal illness with fever, sore throat and cough. A month later he developed pins and needles in the hands and feet, followed by numbness in the extremities. By the time of admission this had spread to the elbows and knees. He then developed unsteadiness on walking which led to frequent falls, but there was no muscular weakness. He also had periodic shooting pains in his legs at night.

There were no symptoms referable to the cranial nerves, and no sphincter disturbance. He gave a long history of winter bronchitis, with cough and mucopurulent sputum, but apart from this he had not had any serious illnesses and there was nothing relevant in his family history.

On examination he was thin but not wasted. The blood pressure was 200/100 mm.Hg, but the heart was not enlarged and the heart sounds were normal. The lungs showed only scattered moist sounds. Nothing abnormal was palpable in the abdomen.

In the central nervous system the optic fundi appeared normal, in so far as lens opacities allowed examination. The pupils were unequal, irregular and failed to react either to light or convergence. Examination of the other cranial nerves showed no abnormality. There was no wasting of the trunk or limb muscles, but the latter were somewhat hypotonic. There was ataxia of sensory type in the upper and lower limbs and marked Rombergism. The tendon reflexes were uniformly absent. Both plantar responses were flexor. Sensory tests revealed a glove and stocking anæsthesia below the level of the elbows and knees. There was gross impairment of position sense in the fingers and toes, and peripheral loss of vibration sense.

The following investigations during his first admission revealed normal blood picture, E.S.R., and urine. The C.S.F. contained 1 cell/c.mm. protein 35 mg./100 ml., globulin not increased, Wassermann negative and Lange curve normal. Blood W.R. and Kahn were also negative. Fractional test meal and glucose tolerance curve were both normal; the urine was examined for porphyrins with negative results. Electromyograms (Dr. Bauwens) showed normal reactions and normal nerve conduction; there was no fibrillation.

He was transferred to Joyce Green Hospital, Dartford, on February 13, 1950, under the care of Dr. Behrman, where nothing additional was found in the history or physical signs, but a biopsy of a sensory nerve showed patchy demyelination. Other investigations, including liver function tests and blood pyruvate tolerance test, were normal. He was treated with vitamin B_{12} injections and injections of dimercaprol without improvement, and was given massage and re-educational walking exercises. He returned to Bethnal Green Hospital on May 26, 1950, and spent the next twenty months there, his condition remaining substantially unchanged. On September 26, 1952, he had a massive hæmoptysis. Following the hæmoptysis he developed a troublesome cough and became very short of breath. During the previous two years he lost 3 st. in weight, his legs had become very wasted and he was unable to stand or walk.

Re-examination revealed no change in the pupils and no abnormality in the

cranial nerves. The upper limbs showed some wasting of the hypothenar muscles and of the interossei. These limbs were hypotonic and when outstretched exhibited pseudo-athetoid movements. Power in the arms was normal. There was gross ataxia in the finger-nose test. The lower limbs were grossly wasted, most marked in the quadriceps and adductor groups, but the calves also were thin. There was marked weakness of the hip flexors and hamstring groups and slight weakness of the quadriceps muscles; power below the knee was normal. There was gross ataxy in the heel-knee-shin test. The tendon reflexes were absent in arms and legs. The plantar responses were flexor. Sensory findings were similar to those of the first admission three and a half years before, although vibration sense and joint position sense were now much more impaired than cutaneous sensation. Position sense was absent in the finger and wrist joints and in the toe, ankle and knee joints. Vibration sense was lost in the upper and the lower limbs, but was normal on the trunk above the pelvis. Light touch appeared to be normal in the upper limbs, but was diminished below the knees and absent in the feet. Cutaneous pain was impaired in an area suggesting C.6 distribution on the dorsal surface of the thumb and index finger extending proximally to just above the wrist. In the legs there was analgesia up to a level one inch below the knees. The soles of the feet were very tender to deep pressure.

Chest examination revealed diminished movements of the right lung with a dull percussion note and a diminution of air entry over the whole of the right lung. There were some scattered rhonchi on both sides. The trachea was deviated to the right. X-ray of the chest showed a dense shadow in the right lung with a little fluid at the base, these appearances supporting the clinical diagnosis of carcinoma of the bronchus.

He lost weight in the ensuing month, but there was no change in the neurological picture. He became somewhat cyanosed and dyspnœic at rest and had further small hæmoptyses.

On November 1, 1952, he developed some pain in the lower abdomen, with difficulty in passing urine, not enough to necessitate catheterization. There was no fever or increase in the tachycardia. The pain persisted, he became enfeebled and died on November 6, four years after the onset of the peripheral neuritis.

The Autopsy Findings

The body was that of a cachectic old man showing marked wasting of the thighs and calves.

The heart showed slight left ventricular hypertrophy. There was some atheroma of the aorta and slight coronary atheroma. There was a large blood-stained right pleural effusion. The right lung contained a bronchogenic carcinoma arising from the right main bronchus. Beyond the growth there was slight bronchiectasis with abscess formation. The growth had extended to mediastinal lymph nodes, but no distant metastases were found. The alimentary tract was normal apart from an abscess cavity of 3 cm. diameter surrounding the appendix which also contained pus; a small focus of caseation was apparent at the proximal end of the appendix. Small areas of caseation were found in superior mesenteric lymph nodes. There was also evidence of fibrocaseous tuberculosis at both pulmonary apices and in the middle of the growth. The kidneys were slightly granular, but otherwise normal. Endocrine glands and the liver were normal.

Sections of the lung showed a typical oat-cell carcinoma of the bronchus; similar growth was present in the regional lymph nodes. The presence of active fibrocaseous tuberculosis in the apices was confirmed. The macroscopic appearance of tuberculosis at the base of the appendix was also confirmed.

C.N.S. and muscles: Macroscopically the brain was normal. The dorsal aspect of the medulla was slightly shrunken and similar appearances associated with

greyish discoloration continued down the posterior columns of the cord. The posterior root ganglia of L.4 and 5 and S.1 and 3 appeared normal.

The right soleus, adductor magnus femoris and psoas major appeared normal. The left sciatic and lateral popliteal nerves also appeared normal.

Histology

Spinal cord.—Weigert-Pal and Loyez stained preparations showed marked demyelination of the posterior columns. In the upper sacral region the central portion of each tractus gracilis appeared intact, the stained areas being symmetrically distributed. In the lower cervical and upper cervical regions there was complete demyelination of the tractus gracilis and partial loss of myelin in the tractus cuneatus, some of the laterally situated fibres of cervical origin being normal in appearance. Marchi preparations showed no evidence of recent degeneration. All other tracts of the cord showed normal appearances of the myelin. Holmes' method of silver impregnation showed loss of nearly all the axis cylinders in the posterior columns with a few persisting fine cylinders in the areas of partial demyelination. Phosphotungstic acid-hæmatoxylin stain showed gliosis of the posterior columns in the cervical region with less marked changes in the lumbar region. Hæmatoxylin-eosin-stained sections showed no evidence of active phagocytosis of lipoid material, the only cells present being scattered microglia and astrocytes with a few oligodendroglia. Myelin bodies were numerous in the areas of degeneration.

Spinal nerve roots and ganglia.—The posterior nerve roots showed complete demyelination in all regions. These degenerated roots on silver impregnation showed a few persisting axis cylinders among parallel rows of Schwann cells. The anterior roots showed normal histological features.

The posterior root ganglia sectioned (L4 and S1) were markedly abnormal. Although some ganglion cells appeared normal others showed various degrees of degeneration. Circumscribed areas of cellular proliferation (the residual nodules of Nageotte) were present around the degenerating neurones and in places only the nodules persisted. Phosphotungstic acid-hæmatoxylin staining showed these proliferating cells to have small vesicular nuclei with dark-staining nucleoli, and pale-staining cytoplasm often prolonged into connecting protoplasmic processes. The latter appeared to support the degenerating ganglion cells in the centre of the nodules, the retracting cytoplasm of the neurones being attached to the connecting processes of the surrounding cells. Sections of the cauda equina showed the degenerative changes of the roots seen elsewhere. There was no evidence of inflammatory infiltration or of malignant deposits.

Brain.—Sections taken from the cerebral cortex, internal capsule, mid-brain and pons showed normal histological features for age. Sections taken through the medulla at the level of the inferior olive showed normal

appearances of the nerve cells 'n the nuclei cuneatus et gracilis. Hæmatoxylin and eosin and toluidine blue sections of the cerebellum showed normal numbers and appearances of the Purkinje and granule cells for age.

Peripheral nerves.—Sections from the left sciatic and lateral popliteal nerves showed bundles of normal fibres (presumably motor) and bundles of degenerated fibres. The lateral cutaneous nerve of the calf consisted largely of bands of Büngner separated by a few surviving axis cylinders.

Sympathetic system.—Sections of the lumbar sympathetic chain and ganglia (L3–5) showed slight lymphocytic infiltration as the only pathological change.

Muscle.—Sections of the right adductor femoris magnus and right soleus showed partial and patchy atrophy of the fibres. The surviving muscle fibres were chiefly smaller than normal but large forms and some normal ones were present. The abnormal forms showed loss of striation and the small fibres showed some loss of staining affinity for eosin and occasional small areas of vacuolation. There was an increase in muscle nuclei most of which were small rod-shaped bodies lying in columns in the sarcolemma and most frequent in the severely atrophied fibres. These nuclei were darkly staining but the vesicular nuclei of the striate substance were also increased in number. A few multinucleate cells of muscle origin and some macrophages containing hæmosiderin were also present.

Between the fibres were adipose cells replacing the atrophied fibres but there was no inflammatory infiltration and little increase in collagen. Holmes' method showed impregnation of the distal portions of the motor fibres in the atrophied muscle groups. Bielchowsky's method showed normal motor nerve endings in the intact and partly degenerated muscle fibres of the adductor femoris. The severely atrophied fibres either showed swollen nerve endings or completely failed to show them owing to the crowded masses of sarcolemmal nuclei. Section of the right psoas showed minimal pathological changes, slight proliferation of the sarcolemmal nuclei, but no atrophy.

Case 2.—A baker's roundsman, aged 59, was first seen at St. Bartholomew's Hospital in August 1950. He complained of an aching pain in the calves of both legs of a year's duration. At first the pain only occurred at the end of the day and was relieved by elevating the legs, but later it persisted during the evening and the night. It became more severe, spread to the thighs and developed a smarting quality which was particularly troublesome at night. For six months he had had pins and needles in the fingers and calves, with shooting pains in the arms. His skin had become very sensitive to light touch, the first areas affected being the forearms and inner sides of the calves. Before admission the pain in the legs became continuous and was most severe in the soles, especially when the feet were warm. At this time he developed some numbness of the skin over the first dorsal interosseal space of the right hand and along the front of the right shin. He had had neuralgic shooting pains in both arms for six months.

He had lost a stone in weight in the past year and complained of ready fatigue and lassitude, with slight breathlessness on exertion.

For twenty-seven years he had had recurrent "lumbago." Two years before he had attended hospital with pain in the right leg, thought to be due to a protruded intervertebral disc at L.1–2, with wasting of the right quadriceps and absence of the right knee-jerk. The pain responded to bed rest, but the other symptoms then became prominent. Apart from this he had had no other illnesses and there was nothing relevant in the family history. His dietary history was normal and he was a teetotaller.

On admission to hospital, on October 28, 1950, he looked somewhat thin and underweight. There was a considerable pigmentation of the exposed parts, attributable to his outdoor work. The heart was not enlarged, heart sounds were normal, blood pressure was 134/80 mm.Hg. No abnormal signs were found in the chest or abdomen. There was some hyperkeratosis of the hair follicles of the legs with old purpuric staining; the skin was somewhat dry and scaly.

Examination of the nervous system revealed nothing abnormal in the cranial nerves and the optic fundi were normal. There was some hypotonia of the limbs and wasting of the interossei in both hands, the right calf and the right quadriceps muscles. These muscles were only slightly weak. Co-ordination was normal. The arm-jerks were present but feeble. The right knee-jerk was absent, but the other tendon reflexes in the legs were normal and the plantar responses were flexor. There was a patchy impairment of sensation to light touch and pain on the right shin and over the right first dorsal interosseus in the hand. Apart from these areas there was marked skin hyperæsthesia especially on the palms and soles, but also affecting the forearms and legs. The calves were very tender. Vibration sense and joint position sense were normal.

Numerous special investigations were done. The only significant findings were a raised blood pyruvate level (1·9 mg./100 ml. on November 8, 1950) and some deficiency of ascorbic acid excretion. X-rays of the chest and alimentary system were normal. C.S.F. was normal in all respects. The fractional test meal showed high gastric acidity. Basal metabolic rate and glucose tolerance curves were also normal.

He was treated with massive doses of vitamins, but no objective change was noted. He was discharged on December 2, 1950, on oral vitamin therapy and seen in the Out-Patient Department monthly.

His condition slowly deteriorated and he complained of a smarting sensation affecting the arms and legs and later spreading to the lower abdominal wall, of stabbing and shooting pains in the limbs, and of pins and needles in the distal extremities. His appetite was poor and his weight fell from 10 st. to 9 st. 3 lb. during three months. He developed progressive numbness of the hands which began in the left and spread up this arm to the shoulder before affecting the right side, and similar numbness in both feet spreading up to the level of the knees symmetrically. The tendon reflexes disappeared simultaneously in the arms and legs.

He was readmitted on April 2, 1951. By this time the numbness had spread up the right arm as far as the elbow. There was considerable clumsiness and weakness of the left hand and some inco-ordination of the right. He also complained of recurrent bouts of hiccough lasting several hours at a time and of weakness of his voice.

On re-examination he was more cachectic than on the previous admission and showed the following changes in his neurological condition. In the arms the left triceps muscle had become weak, but there was no further weakness or wasting of the legs. The tendon reflexes were absent in the arms and legs, but the plantar responses remained flexor. The calves were still very tender on palpation and the gait had become ataxic. Sensation to pin-prick was absent below the elbow in the right arm and below the shoulder in the left arm. Joint position sense was grossly impaired in the right fingers and absent in the left wrist and fingers. Vibration

sense was absent below the level of the elbows on both sides. In the legs there was symmetrical loss of pain below the level of the patellæ and fading loss of light touch, most marked distally below mid-calf. Position sense was impaired in the halluces but vibration sense at this time was still normal in the legs.

The alimentary tract was found to be normal on barium X-ray, but chest films and screening were thought to be somewhat doubtful. Because of this bronchoscopy was done on August 2, 1951, but apart from slight excess of mucus on the right side nothing abnormal was found. Bronchography on August 18, 1951, also showed nothing abnormal. Blood count revealed only slight hypochromic anæmia, with a normal white cell count and differential. Sternal puncture showed an increased erythropoiesis of normoblastic type, but no malignant cells were seen. The C.S.F. was re-examined and contained excess protein (100mg./100ml.) with a slight excess of globulin. In other respects it was normal. The urine contained neither Bence-Jones protein nor prophyrins. Pyruvate tolerance test (Professor Thompson) fasting 0·9 mg.; 90 mins after test dose 1·27 mg./100 ml., both within normal range.

During the six-month period of his second admission, the chief features noted were a slow spread of the level of sensory loss up the arms, taking about a month to spread an inch. By July 1951 this level had reached to the mid-arm area on the right and shoulder level on the left, and to mid-thigh on both sides, and thereafter remained stationary till his discharge. Cutaneous hyperæsthesia was marked over the abdominal wall. He was just able to hobble unsteadily about and his arms also were inco-ordinate.

He was treated with crude liver extract, dimercaprol and later with co-carboxylase, but there was no objective change in the neurological signs.

He was discharged from hospital on September 18, 1951. After this the anæsthesia spread up the right arm and became denser in all the extremities and he developed more wasting of the legs.

In February 1952 the pains became so severe that he was readmitted to hospital. He had been unable to walk for the preceding eight months and there was now marked hyperæsthesia of the face and some weakness of grip in both hands.

Clinical and X-ray examination still revealed nothing abnormal in the chest. Wasting had extended to the upper arms but there was little muscular weakness. There was gross wasting of both thighs and calves. Sensory testing showed that there was marked hyperæsthesia to pain and light touch in the trunk and a level of cutaneous anæsthesia at the shoulder and upper third of the thigh. Vibration was not appreciated below the costal margin or in the upper limbs. Position sense was absent in all joints in the upper limbs and in the joints of the legs below the knees. E.S.R. was 6 mm. first hour (Westergren), and hæmoglobin 11·8 grammes/100 ml.

He was very depressed during this last period of his illness. The severe limb pains necessitated large doses of physeptone and pethidine. He became grossly cachectic and somewhat cyanosed and more anæmic, the hæmoglobin falling to 8·7 grammes/100 ml. and red cells to 3·48 million/c.mm.

He died suddenly on April 19, 1952.

The Autopsy Findings

The body was that of an old man showing wasting of muscles of the extremities, but no loss of subcutaneous fat.

There was an early fibrinous pericarditis. The valves and orifices of the heart were normal but the left coronary artery was markedly atheromatous and almost completely occluded at one point. The right coronary artery was also atheromatous The myocardium, however, appeared normal, there being no evidence of infarction.

The right lung contained a large bronchogenic carcinoma arising from the lower lobe main bronchus and spreading into the parenchyma and into the tracheo-

bronchial lymph nodes. Peripheral to the growth there was collapse and œdema. The right lower lobe showed the macroscopic appearances of early bronchopneumonia. The pleuræ appeared normal.

The alimentary tract showed normal post-mortem appearances of the stomach, intestines and pancreas. The liver showed the changes of chronic venous congestion but no evidence of metastases. The spleen and adrenals appeared normal.

A section of the lung tumour, kindly provided by Dr. Hopkins, Pathologist at Bethnal Green Hospital, showed a typical oat-cell carcinoma of the bronchus.

C.N.S.—Macroscopically the brain was normal but the spinal cord showed greyish discoloration of the posterior columns. Loyez-stained sections of the lower lumbar region showed symmetrical demyelination of the posterior columns, the medial portion of the tractus cuneatus on each side appearing intact. Marchi preparations showed recent demyelination of the medial and lateral parts of the tractus cuneatus but there was no evidence of recent degeneration elsewhere. Hæmatoxylin and eosin stained sections showed degeneration and gliosis of the posterior columns, the latter finding being confirmed by phosphotungstic acid hæmatoxylin preparations. The posterior columns also contained numerous myelin bodies and a few fat phagocytes. Holmes' method showed degeneration of most of the axis cylinders in the areas of demyelination.

Section of the nerve roots and posterior root ganglion of S.1 showed gross degeneration of the ganglion cells and replacement by residual nodules. These were composed of concentric rings of small darkly staining cells with scanty cytoplasm. The nerve roots were surrounded by bands of acellular collagen and numerous myelin bodies. Sections stained by Loyez's method showed complete demyelination of the posterior roots but normal appearances in the anterior roots. The posterior roots consisted of parallel bands of Schwann cells and a few remaining axis cylinders.

Sections of the sciatic nerve prepared by the modified Weigert-Pal and Loyez methods showed demyelination of some bundles with intact sheaths in others. The axis cylinders in the demyelinated fibres had degenerated but those in the myelinated fibres appeared normal.

Striated muscle.—Sections of calf muscle showed mild atrophic changes. A few degenerating fibres were present with small areas of fibrous replacement. The abnormal fibres were mostly narrower than normal but occasional large forms were present. Both types of fibres showed slight loss of striation and affinity for eosin, but no vacuolation. Nuclear proliferation was moderate and affected the sarcolemmal nuclei which were arranged in chains and columns along the narrow degenerating fibres. A few large nuclei were present but syncytial masses were not seen. Holmes' method showed axis cylinders in the small nerve bundles in the muscle, but failed to demonstrate the terminal portions of the motor fibres.

Case 3.—A carpenter, aged 65, was referred to the Neurological Out-patients at Croydon General Hospital in September 1951, and admitted to St. Bartholomew's Hospital on October 11, 1951. He complained of difficulty in walking, which began three months before when he noticed that the feet were weak at the ankle and that his toes were apt to catch the ground. Later he noticed weakness in rising from a chair and his legs tended to give way on descending stairs. As well as the weakness he had become unsteady on his feet, especially on turning. His grip had also become weak. There had been no sensory symptoms.

He gave a thirty-year history of chronic bronchitis, worse in winter months. One and two years previously he had attacks of acute bronchitis each lasting two weeks. In the second of them the sputum was streaked with blood. During the past year he had developed progressive exertional dyspnœa, his appetite was poor,

his dietary intake poor and he had lost a stone in weight. For a month there had been some dysphagia with food "sticking" behind the sternum.

On examination he was somewhat sallow and wasted. The tongue was red and glazed and there was some koilonychia. The chest was barrel-shaped with scattered added sounds, but no signs of consolidation. The heart and abdomen were normal, blood pressure 155/95 mm.Hg.

In the central nervous system the cranial nerves were normal; the arms showed generalized wasting but power was normal apart from some weakness of grip. Both legs showed marked wasting and tenderness of the calf muscles; there was considerable weakness of the hip flexors and extensors and also of the extensors of the feet. His gait showed a wide-based ataxia and Rombergism. The tendon reflexes were sluggish in the arms, the knee-jerks only just obtainable and the ankle-jerks absent. Plantar responses were flexor. Cutaneous sensation was normal apart from some impairment of pin-prick over the front of both shins. There was distal impairment of vibration sense in the legs, but position sense in the fingers and toes was normal.

X-rays of chest showed a large hilar mass on the right side with some collapse of the right upper lobe. Barium swallow showed narrowing of the œsophagus with delay at the level of the hilar shadow. Bronchoscopy on October 24 showed some narrowing of the right main bronchus and gross narrowing of the right upper lobe orifice. There was no visible neoplasm and biopsy was not possible. Œsophagoscopy showed some narrowing of the junction of upper third and lower two-thirds but no neoplastic tissue.

Blood count showed a mild hypochromia, Hb 11·0 grammes/100 ml., R.B.C. 5·1 million, white cell count and differential normal. Blood Wassermann was negative, E.S.R. (Westergren) 37 mm./1 hour. C.S.F. showed 3 lymphocytes per c.mm., protein 45 mg. per 100 ml.; other constituents normal. Fractional test meal showed a complete histamine-fast achlorhydria.

Pyruvate tolerance tests showed a raised fasting level of 1·23 mg. and the 60 and 90 minutes after glucose were 1·42 and 1·71 mg. respectively.

He was treated with intravenous thiamine 100 mg., riboflavine 50 mg. and nicotinic acid 200 mg. daily for two weeks and there appeared to be some improvement in the neuropathy. Sensation returned to normal and tenderness of the calves disappeared and the ankle-jerks returned. The proximal weakness of the legs persisted, however, and his ataxia was little improved. The pyruvate tolerance test was repeated and the figures were: fasting 0·93 mg., 60 minutes 1·29 mg., 90 minutes 1·45 mg. per 100 ml.

The bronchial neoplasm was treated with deep X-ray therapy which the patient did not tolerate well. He developed a severe chest infection and treatment had to be discontinued after three weeks. The infection was treated with chloramphenicol and he was discharged on December 21, 1951.

After returning home he deteriorated slowly, continuing to lose weight and taking little solid food. He was at first able to walk with crutches, but one month later he was unable to stand or walk and for some months he led a wheelchair existence. His legs became extremely wasted, out of proportion to the general emaciation. There was no complaint of numbness or paræsthesiæ, but he complained of some weakness of the left upper limb although the power in the right upper limb was normal.

He was admitted to a local hospital on July 28, 1952, and died on August 20, 1952. He was not re-examined neurologically and no post-mortem was held.

Case 4.—A lathe operator, aged 54, was referred by Dr. Philip Buckley (to whom we are indebted for much of his subsequent history) to Dr. Aldren Turner at St. Bartholomew's Hospital on April 24, 1951, and was admitted on May 24, 1951. He gave a fourteen-month history of dull aching pain in front of the right thigh

which was at first only present while walking and lifting up the leg on to the curb. A few weeks after the onset a similar but milder pain began in the left thigh. Both pains persisted unchanged from the onset.

Soon afterwards he noticed a certain "loss of mobility" in the right thigh and soon both thighs became noticeably weak, the main difficulty being getting up and down stairs. For a year he had been unable to run and for nine months had difficulty in getting up from a seated and lying position. The muscular weakness was somewhat variable from day to day and was more marked in the evenings. At times it seemed to him that he had to wait for the muscles to contract. There were no sensory symptoms. Sphincter control was normal. He did, however, complain of dryness of the mouth. He had had kyphoscoliosis since about the age of 15, although this had not caused him any disability. In the 1914–18 War he had sandfly fever, malaria and dengue.

On examination he looked healthy though he was somewhat obese.

Central nervous system examination.—The cranial nerves and the fundi were normal. Power, tone and co-ordination were normal in the arms. He had considerable difficulty in getting up from a lying position, owing to weakness of the hip flexors. There was slight wasting of both thighs. The hip flexors, adductors, glutei and hamstrings were slightly weak and quadriceps were moderately weak. All muscles below the knee were normal in power. Tendon reflexes were sluggish in the arms and the knee and ankle jerks were absent. Plantar responses were flexor. Superficial sensation was normal but vibration sense was diminished in both legs up to and including the pelvis. The cardiovascular, respiratory and alimentary systems were all normal. Injection of neostigmine 1·5 mg. produced a dramatic effect, the patient becoming able to walk normally and rise from a seated position without difficulty. He still had difficulty in getting up from the lying position. When the injection was repeated the following day the effect was less marked. Electrical reactions showed partial R.D. in the vasti and there appeared to be abnormal fatigability to stimulation.

Biopsy of the calf muscle showed most of the muscle fibres to be normal. There was splitting and fragmentation of a few fibres with proliferation of the sarcolemmal nuclei. Cross striations were normal and the cytoplasm showed no evidence of vacuolation or granularity. The nerves and blood vessels appeared normal.

X-rays showed nothing abnormal in the chest, but a scoliosis of "structural" type with wedging of the thoracic vertebræ.

He was discharged on June 14, 1951, on oral neostigmine 30 mg. three-hourly with atropine grain 1/100 t.d.s. When given a total daily dose of 150 mg. of neostigmine he was considerably improved but still complained of some weakness of the legs first thing in the morning lasting for half an hour.

He was seen a month later when his condition was less satisfactory than might have been expected in a case of myasthenia gravis. He still lacked energy and complained of pains in the back and in both thighs and legs. His muscles were somewhat weak especially on waking and towards the evening, but he had been able to return to light employment to which he walked from his home half a mile away.

Five months after discharge there was some weakness of the hip flexors but the quadriceps were normal; knee and ankle jerks were still absent. On January 25, 1952, he was much the same, but was now able to get up from sitting in a chair and also get up from lying down flat. The only muscular weakness was in the hip flexors. The ankle-jerks were now easily obtainable and the knee-jerks present with reinforcement.

He was last seen on April 18, 1952, when he was still improving. The legs were stronger and he was able to walk more than a mile and was working full time. On

examination the hip flexors showed only minimal weakness and all the other muscles were normal. The knee and ankle jerks were brisk and equal.

On October 5, 1952, he was admitted to Chelmsford Hospital after a hæmoptysis. X-rays of the chest showed a carcinoma of the right upper lobe. Mr. Geoffrey Flavell had performed a bronchoscopy and proved the diagnosis. Although the carcinoma was an advanced one, there was now no leg weakness and the reflexes were normal. At the time of writing this patient is still alive.

Comments

The bronchial carcinoma.—In each case the bronchial carcinoma had spread to the regional lymph nodes, but there were no distant metastases. Including our 2 cases in which histological material was available, of the 15 cases of neurological disorder accompanying carcinoma of the bronchus in which the histology of the growth is recorded, 11 are described as oat-cell in type, 3 as squamous and 1 as undifferentiated. Most of these cases spread only to the regional nodes, although one of Denny-Brown's cases had a metastasis in the stomach. Russell Brain, Daniel and Greenfield (1951) described adrenal deposits in their Case 4 and the oat-cell growth described by Parkes Weber and Hill (1933) showed widespread blood-borne metastases.

There was a very long time-interval between the onset of the peripheral neuropathy and the first symptom of the carcinoma, in both Case 1 and Case 2 nearly three years and in Case 4 eighteen months. Kremer and Pratt report a similar case with a two-and-a-half year interval. Although the neurological picture in Cases 1 and 2 recalled Denny-Brown's cases and led to investigation of the chest in both, including bronchoscopy and bronchography in Case 2, no evidence of bronchial neoplasm could be obtained. In Case 4, the patient's muscular power progressively improved and the reflexes returned, but eighteen months later the lung lesion became manifest. Only in Case 3 was the presence of the carcinoma not in doubt when the patient was first seen.

Classification of neurological changes.—Apart from metastatic deposits, either blood borne or in the meninges, the following degenerative disorders of the nervous system occur in association with carcinoma of the bronchus:

Sensory neuropathy.

Mixed motor and sensory neuropathy.

Myopathy.

Cerebellar degeneration (with or without dementia).

These may be combined in any one case; a common association is a sensory neuropathy with myopathy, as in Case 1, and another cerebellar degeneration with sensory neuropathy. From the literature it would appear that a mixed sensory and motor neuropathy is the commonest type, but the true incidence of the various types is not yet known.

Sensory neuropathy.—The clinical findings in Cases 1 and 2 were different from 3 and 4 and resemble closely the two patients described

by Denny-Brown and simultaneously by Wyburn Mason, also the earlier case of Parkes Weber and Hill, and that of Kremer and Pratt. In all these patients there was a disorder of the peripheral sensory system, maximal in the lumbosacral and lower cervical roots, but also affecting to variable extent the trunk and trigeminal distribution. The onset of the condition may be very gradual, progressing slowly over a period of months or years, or it may come on subacutely after a febrile illness and reaching a maximum in a few weeks, thereafter remaining stationary. There may be periods in which the symptoms lessen, and the areas of sensory loss recede, and this may be shown histologically by gliosis in the tracts involved.

Once developed, the patient is deafferented and sensory ataxia is severe. There is often a greater loss of joint position and vibration sense than of cutaneous sensibility, and although a glove and stocking type of anæsthesia is usual, on careful testing evidence of a radicular pattern may be found—this was present in both our patients: in Case 1 the anæsthesia of the arms was restricted to a strip corresponding with C 6 root, and in Case 2 sensory loss began in areas suggestive of C 6 and L 4 dermatomes. The tendon reflexes were first diminished and later absent. Root pains of a shooting and burning quality were present in both patients, and in the first were mistaken for the lightning pains of tabes dorsalis. In the second patient, they had the quality of the "burning feet" syndrome seen in prisoners of war, and although the latter has been attributed to pantothenic acid deficiency (Smitskamp, 1947) it is of interest that there was no response to massive doses of parenteral calcium pantothenate. In this patient cutaneous hyperæsthesia was very marked and was present early in the areas later showing sensory loss, which replaced it, and it persisted unchanged on the trunk and face till death.

The symmetrical and extensive degeneration of the posterior columns of the cord and of the posterior nerve roots is inexplicable on the grounds of a single or of multiple scattered anatomically localized lesions, and appears to represent a systematized degenerative disorder. Both cases described above showed various degrees of degeneration of the posterior root ganglion cells sufficient in both cases to account for the peripheral and centripetal degeneration of the neurones. None of the numerous sections of the brain, cord or nerves showed metastases. In both cases gliosis of the posterior columns was well marked. Neuroglial proliferation in the degenerated areas was recorded previously by Parkes Weber and Hill in the posterior columns, by Greenfield (1934) in the nucleus of Luys and by Russell Brain *et al* in the cerebellum in two cases. In spite of the degree of involvement of the nerve roots, there was no pleocytosis and little alteration of protein in the cerebrospinal fluid.

Mixed motor and sensory neuropathy.—A mixed type of peripheral neuritis, of fairly sudden onset, fluctuating in severity, was described by Lennox and Prichard and has been observed by Elkington and Henson

(1953); Case 3 is of this type. The duration of the illness in the Hammersmith series varied from two to fifteen months. In 2 cases death was due to respiratory failure from rapid spread of the motor weakness, which was a marked feature of their cases, and facial paralysis and dysphagia also occurred. Sensory changes were slight and areflexia a late sign. In 3 of their cases the peripheral neuropathy improved, death resulted from the carcinomas and examination of the spinal cord was normal. In one of their cases there was histological evidence of peripheral nerve degeneration, chiefly motor, and the muscles showed neural atrophy.

Muscle changes.—Denny-Brown thought that the muscular changes he found histologically were clinically latent, but there was marked weakness of the hip and knee muscles in his first case with wasting of the musculature of both thighs. In our Case 1 there was marked atrophy of the lower limb muscles with weakness chiefly of the psoas, quadriceps and hamstrings. In the second patient wasting of the thighs and calves was also present, though late in appearance; there was little, if any, muscular weakness. In all these patients the myopathic changes appear to have been restricted to these muscles of the lower limbs.

The histological changes in Case 1 were similar to those of Denny-Brown's cases. The patchy distribution of the degenerative changes with loss of striation and irregular affinity for stains resemble the lesions of a primary muscular dystrophy rather than a neural lesion (Rabinovitch *et al*, 1951). In Case 2 the only obvious change was an increase in the number of the nuclei.

Although the peripheral nerves sectioned show degeneration of some fibres and normal appearances of others, the fact that a cutaneous nerve is almost completely destroyed, that the posterior roots at all levels of the cord are degenerated and that the corresponding anterior roots are intact, show that the motor nerves as a whole are normal. Holmes' method has impregnated axis cylinders in small nerve bundles and occasional single fibres close to muscle fibres. These are presumably motor, and this is further supported by the demonstration of motor nerve endings in partly degenerated muscle fibres of adductor femoris of Case 1. Careful examination of the peripheral nerves and of the anterior nerve roots has failed to show the narrowing of the myelin sheaths and axis cylinders in the internodeal areas as described by Denny-Brown. In the literature the two cases of Denny-Brown already referred to are the only ones with similar muscle changes.

In neither of our cases do the lesions appear as acute as in the muscles of experimental vitamin-E deficiency. Denny-Brown suggested that the cause of the muscular changes in his cases might be a conditioned deficiency of this vitamin. The histology in our cases is also quite distinct from the menopausal myopathy described by Shy and McEachern (1951) which these authors state responds to vitamin E therapy. A further possi-

bility is that the muscle changes could be due to disuse atrophy, but we have been unable to find in the literature any reference to this appearance in it. We are at present investigating this point.

We do not think, therefore, that the muscular changes can be explained by a conditioned vitamin-E deficiency, or by disuse or neural atrophy, and believe that the degree of the change in Case 1 is very suggestive of a primary myopathy.

A very unusual feature of the fourth patient was the response to neostigmine, although this was somewhat variable; the biopsy changes were minimal. The diagnosis in this patient was obscure, but he was thought to be suffering from an atypical myasthenia gravis or a late myopathy, although the loss of vibration sense could not be explained on this basis. By the time the bronchial neoplasm was obvious clinically, the previously absent leg reflexes had returned and there was no muscular weakness.

A further case one of us has seen recently showed myotonia, both on active movement and on percussion, this being associated with a mixed peripheral neuropathy and a round pulmonary neoplasm. The myotonia responded well to quinine. Worster-Drought and Sargent (1952) have recently described a case of recovering peripheral neuropathy showing myotonia.

Cerebellar and cortical regeneration.—The last peculiar neurological association with bronchial carcinoma is a subacute cerebellar degeneration. This, first described by Greenfield (1934) and later by Brain, Daniel and Greenfield (1951), may also be seen in association with carcinoma of the ovary, breast and uterus. In this syndrome, as well as the cerebellar signs, a dementia may ensue and shooting pains in the legs with areflexia occur, together with degeneration of the posterior columns. Unlike the polyneuritic group there is a pleocytosis in the cerebrospinal fluid attributable to inflammatory changes in the cerebellum, but the pain and areflexia would seem to link the cerebellar syndrome with the cases we have been describing.

Nature of the association.—The nature of the association has already been discussed by Denny-Brown, Lennox and Prichard, and Wyburn-Mason, and our studies provide little that is new. It seems clear that metastases will not account for the anatomical lesions. Of possible metabolic causes malnutrition is not a factor, as our patients did not lose weight until the neuropathy was well established; their appetites and food intake were normal. In Case 3 there was some dysphagia from œsophageal compression, but this was a late symptom. A primary carcinoma of the œsophagus with a sensory neuropathy similar to Cases 1 and 2 has been described recently by Dodgson and Hoffman (1953) In both of our cases the fractional test meal was normal. None of our patients had any diarrhœa. As regards specific vitamin deficiencies,

blood pyruvate estimations were normal in the first case, slightly raised early in the disease in the second but reverting to normal later, and definitely raised in the third patient. In view of the lack of consistency in these findings their significance is doubtful. All 3 patients with the neuritic type of disease received large parenteral doses of vitamins of the B group also with inconsistent results. 2 were treated with dimercaprol but without any benefit.

While we are in agreement with the views of the previous authors that the association between the two conditions must lie in some derangement of metabolism, it seems probable that the cause is not single. The range of clinical disorders, primary sensory, motor neuritic, myopathic, myotonic, myasthenic, cerebellar and dementing, seen in association with bronchial carcinoma is very wide, and it may well be that many factors play a part.

In all patients in the later age groups with symptoms of peripheral neuropathy or obscure muscular disorder, carcinoma of the bronchus must be remembered. The primary sensory neuropathy is, in our opinion, so characteristic of the syndrome that even if the chest X-rays show nothing abnormal, bronchoscopy should invariably be performed. Russell Brain (1951) and Lennox and Prichard have both reported improvement after removal of the growth.

Summary

(1) Two cases of peripheral sensory neuropathy, one with myopathic changes, one case of mixed peripheral neuropathy and one case of an obscure myopathy are described.

(2) All cases were associated with carcinoma of the bronchus.

(3) Full post-mortem and histological features of one case and limited pathological features in the other sensory neuropathy are described.

(4) The clinical and pathological features of the cases are compared with those recorded in the literature.

(5) The necessity for thorough chest investigation in all cases of peripheral neuropathy or myopathy in the older age group is stressed.

Acknowledgments

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PLATE III

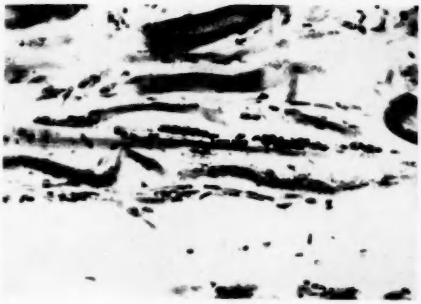

FIG. 1

FIG. 2

FIG. 3

FIG. 4

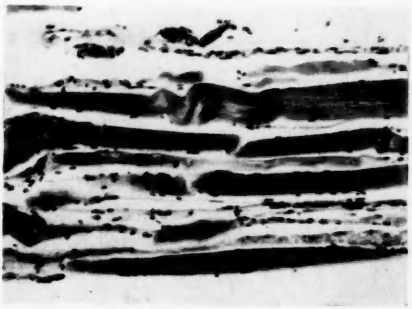

FIG. 5

To illustrate article by K. W. G. Heathfield and J. R. B. Williams

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PLATE III

LEGENDS FOR FIGURES 1—5

FIG. 1 (*Case* 1).—Soleus muscle. Microphotograph showing narrowing of the fibres, increase in nuclei and loss of striation. × 400. Hæmatosylin and eosin.

FIG. 2 (*Case* 2).—Cervical cord. Microphotograph showing demyelination of posterior columns and posterior roots. × 7½. Loyez.

FIG. 3 (*Case* 1).—Posterior root ganglion, S.1. Microphotograph showing demyelination of posterior root, proximal and distal to the ganglion with myelinated anterior roots at one side. × 10. Modified Weigert-Pal.

FIG. 4 (*Case* 1).—Gastrocnemius muscle. Microphotograph. × 180.

FIG. 5 (*Case* 1).—Adductor femoris muscle. Microphotograph. × 180.

A STUDY OF MYOCLONUS

BY

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THIS paper is based on a clinical study of 6 patients with myoclonus and its purpose is to record, analyse and discuss the nature of the involuntary movements which were observed.

So many different neurological entities have been called myoclonus that it has been difficult to distinguish the condition from other myospasms. The term is here understood to mean "A disturbance of neuronal activity characterized by very sudden involuntary jerks, which are arrhythmic and asynergic, involving portions of muscles, whole muscles or muscle groups." This is a clinical definition and it may not be possible to ascertain whether these jerks are synchronous or asynchronous. Further it is concerned alone with the quality of the myospasm; the magnitude may be as small as the twitch of a fasciculation or, if the legs are affected, the patient may be thrown to the ground. It is not proposed to discuss involuntary movements which do not fulfil this definition. Particular amongst those maladies which have been hitherto called myoclonus is the syndrome of velo-palato-laryngeal myoclonus. The rhythmic nature of the muscular contractions which are observed is distinct from the quality of the myospasm that is here considered. Moreover the localization of the causative pathology has been shown by Klingler (1949) and others to be the central tegmental tract or the bulbar olive. This site has not been incriminated in the production of arrhythmic myoclonus, so that there is both clinical and anatomical evidence to justify the exclusion of this syndrome from the myoclonias. It would serve to clarify the issue if myoclonus was used to describe conditions within the scope of the present definition.

When myoclonus is diffuse and small in amplitude it may resemble fasciculation. Interruption of the appropriate final common pathway with a local anæsthetic will abolish myoclonus whilst fasciculation will persist. In addition, uncomplicated myoclonus is not accompanied by electromyographic evidence of damage to the lower motor neurone.

Myoclonus, without epilepsy.—In 1881 Friedreich described Paramyoclonus Multiplex, a chronic condition of adults who exhibited no other signs of organic disease. It was characterized by asynchronous

myoclonus involving the trunk and proximal limb segments. These contractions were diffuse, seldom producing displacement of the limbs and recurred in salvos of 40–50/minute. They were maximal at rest, disappeared during sleep and were provoked by emotional and tactile stimuli. More recent descriptions include those of Walker and Chaney (1946) and Morris (1947). This is a rare and benign condition and the literature affords only one full autopsy report (Ramsay Hunt, 1903) in which it is recorded that no unequivocal lesion in the nervous system was detected.

Though myoclonus is more commonly associated with other abnormal neurological signs the publications of Langdon (1902), Reid (1927) and Morris (1947) have shown that it may also be a transient and isolated phenomenon.

Myoclonus-epilepsy.—Many epileptic patients experience occasional myoclonic jerks (Gowers, 1881) and the incidence of this symptom has varied from 15–70 per cent (Hodskins and Yakovlev, 1930; Reynolds, 1861). The familial syndrome of myoclonus, epilepsy and dementia was reported by Lundborg (1903). This malady, which commences in childhood, runs a progressive course in ten to twenty years terminating in rigidity and decubitus. Since that time familial myoclonus without dementia or without epilepsy has been observed.

In 1921 Ramsay Hunt described Dyssynergia Cerebellaris Myoclonica; a cerebellar ataxia with myoclonus-epilepsy. The frequency of physical signs indicative of a lesion of the cerebellum or its connexions has since been stressed and though these may be minimal they were detected in nearly one-third of a large series of patients with myoclonus-epilepsy (Hodskins and Yakovlev, 1930).

Minor variations in the character of the involuntary jerks have been recorded. Though most often they involve agonist muscles during contraction, André-Thomas, Ajuriaguerra and Boitelle (1944) observed myoclonus which was confined to the antagonists. Goodkind (1936) provoked the jerks with light, Gastaut and Remond (1952) by acoustic stimulation and Dawson (1947) by muscle stretch.

Van Bogaert (1950) has reviewed the pathological conditions which may be associated with myoclonus. He divides these into two groups. The cerebellar degenerations, heredo-familial ataxias and lipidoses comprise the first, whilst the second includes various encephalitides, vascular occlusion, toxic and biochemical disturbances.

The localization of the causative lesion remains unsettled. However in all 12 of the cases reviewed by Hodskins and Yakovlev, in which a full histological examination had been made, the region of the dentate nucleus was involved and these findings are in agreement with the observations of most other workers.

Case Reports

Six cases of myoclonus are presented and for the sake of brevity, for the most part, only positive physical signs are recorded. None of the patients experienced pain or paræsthesiæ during the times when they had involuntary jerks. Questioning of patients and their relatives showed that, with the exception of Case 1, no other member of their families suffered from diurnal or nocturnal myoclonus.

Under the heading "Observations on the Myoclonus" it is recorded that certain sensory stimuli were applied in an attempt to provoke the involuntary jerks. To avoid unnecessary repetition "passive muscle stretch" has been used to include all of the following: Sudden passive displacement of the limbs at large joints, repetitive tendon percussion and repetitive muscle percussion. By "thermal stimuli" is meant immersion of the patient up to the neck in water at temperatures of 45° F. and 110° F. for ten minutes at a time.

Case 1 (*No.* 41897). *F. C., female, aged* 69 (*a housewife*).

The patient, who was admitted 10.2.53 under the care of Dr. Denis Williams, had enjoyed good health up to the age of 30, when she noticed shakiness of her hands, unsteadiness in walking and difficulty in articulation. These symptoms commenced insidiously and were slowly progressive up to the time of her admission to hospital.

The tremor of her hands was minimal at rest and became most pronounced when she moved her arms or hands. It was particularly severe when she was tired or nervous or when she was startled (for instance by an unexpected knock at the door). In addition to this tremor she had difficulty in performing tasks requiring fine movements of the fingers.

Her gait was so unsteady that she staggered from side to side, though she never fell down. Articulation during this time became slurred and was interrupted by muscular twitches around the mouth and lower face. None of her disabilities could be related to external factors and they varied in severity from day to day.

At the age of 48 she was investigated in a local hospital where a lumbar puncture was performed. The cerebrospinal fluid was normal and the Wassermann reaction in blood and fluid was negative. She was diagnosed as a case of disseminated sclerosis and given fever therapy without effect.

At the ages of 55 and 68 she had two periods of depression lasting three to six months. The first followed the death of her husband; the second occurred when her son left home and she was living alone in the house.

During the last year she noticed sudden involuntary jerks of her arms and legs, which she described as "the fidgets." These occurred only during movement with variable severity from day to day. She was never wakened by them and she performed her household duties without assistance.

Her past medical history was irrelevant. She was the fifth child of healthy parents and had three healthy children of her own who are aged 41, 39 and 38 respectively.

Her son, aged 38, had two children, the eldest of whom was said to have died at the age of 1 year from Hoffmann's spinal paralysis. A child of her elder brother was diagnosed in 1929 at the age of 18 as suffering from spasmodic torticollis. He is now aged 42, and, according to the patient, suffers from a condition very similar to her own. This is characterized by tremor of the hands, sudden jerking

movements of the limbs, unsteadiness in walking and slurred speech. He is unfortunately unwilling to submit to examination.

Apart from these instances the family is free from neurological disease and skeletal deformities.

On examination she was found to be emotionally labile, but of average intelligence. Routine examination of the cranial nerves, special senses and sensory system revealed no abnormality. In particular there was no nystagmus. Development and power were normal. With both arms supported at rest there was a bilateral coarse rhythmic tremor at a rate of 1–2/second involving the finger flexors and extensors, the thumb and to a lesser extent the pronators and supinators of the forearms, which was most marked on the right side. On voluntary movement this tremor disappeared but after a few seconds returned and was more marked. A similar tremor involved the toes of both feet. The outstretched hands showed occasional slow athetoid movements especially on the right. Finger-nose-finger, heel-knee-shin, and finger-to-finger tests revealed a moderate inco-ordination and irregularity of performance. Voluntary movement was occasionally interrupted by a sudden involuntary jerk of the limb in action. Resistance to passive stretch was less than normal. The deep tendon reflexes were all present but difficult to obtain, the abdominal reflexes were preserved and the plantar responses flexor. Gait was moderately ataxic on a wide base. There was no Rombergism and general examination demonstrated no abnormality other than a blood pressure of 210/120 mm.Hg.

Observations on the myoclonus.—No involuntary jerks were observed when the patient lay at rest and the muscles were only involved when they were in a state of voluntary or involuntary contraction. At such times occasional sudden jerks, which were arrhythmic and asynergic, affected those muscles. These included the lower facial muscles, particularly the orbicularis oris, the masseters, the tongue, sternomastoids and trapezius. In the upper limbs the deltoid, triceps and biceps were involved and in the legs the plantar flexors of the ankles and toes. Such contractions caused elevation and abduction of the shoulders, flexion of the elbows with slight supination aud plantar flexion of the ankles and toes. The jerks were infrequent recurring every two to ten minutes, except over the face, where during speech they were almost continuous, causing jerky irregular vocalization.

At no time of the day were they especially pronounced neither were they observed during sleep, nor in the periods immediately following or preceding sleep, when the patient was relaxed. Passive muscle stretch, tendon and muscle percussion, repetitive pin-prick and startle failed to provoke the myoclonus. The jerks occurred more frequently if an action was performed rapidly rather than slowly and if the patient suddenly changed the direction of a movement. When she was anxious, the myoclonus was more severe but no other predisposing factor could be identified.

Investigations.—X-ray of chest and skull were normal. Electroencephalogram (report by Dr. W. A. Cobb): There is an 8–9 c/s alpha rhythm which blocks on eye opening. A moderate amount of rather low voltage 4–7 c/s activity appears at random. Recurrent complexes consisting of four or five 8–9 c/s waves superimposed on a slow wave appear in the temporal-central region on either side, but more often on the left. During over-breathing sharp waves were also seen in the temporal areas. These are rather mild abnormalities of an unusual type seen in the temporal-central area mainly on the left. There is no evidence of a focal lesion at a corical level.

Comment.—This case illustrates the association of cerebellar signs with myoclonus in the absence of clinical epilepsy or mental deterioration. The age of onset and the history of a similar condition in a nephew suggests that an abiotrophy is concerned in the production of these symptoms.

Case 2 (*No.* 36545). *M. E. F., female, aged* 54 (*a housewife*).

The patient was admitted 14.2.52 under the care of Sir Charles Symonds.

She had been in good health up to February 1951 when her daughter was admitted to a chest hospital with pulmonary tuberculosis. Shortly afterwards the patient felt tired and depressed. She noticed that two or three times a day, whilst she was walking, her legs suddenly gave way under her. One month later she became aware of sudden involuntary jerks of her arms and hands. These were infrequent and usually occurred when she was brushing her hair. She also noticed that her speech became jerky and hesitant and at these times involuntary twitches involved her lower face, lips and tongue which were sometimes so severe that phonation was arrested. All these symptoms varied in severity from day to day and were especially marked when she was nervous. She lost confidence in herself and refused to use the stairs or walk outside the house unless she was supported. In April 1951 she was admitted to Guy's Hospital and after two weeks with sedation and rest is said to have made a complete recovery. She remained well for several months until she had a minor fall. After this her symptoms returned and she again lost confidence in herself. In January 1952 she fell again and a further exacerbation of her symptoms occurred.

Her past history included a right facial palsy at the age of 50 which cleared up within six weeks. Her family had no neurological complaints and there were no skeletal deformities amongst her siblings.

On examination she was a middle-aged woman with greying hair of average development. There was evidence of slight mental deterioration since her admission to Guy's Hospital, but her grasp of everyday affairs was fairly good and she was fully orientated in time and space.

There was no abnormality of the special senses. Speech was slow, jerky and irregular and was accompanied by twitching of the facial muscles, particularly around the left angle of the mouth. Apart from this the cranial nerves were intact.

In the limbs there was slight weakness of the small muscles of the right hand and of the long extensors of the fingers on that side. Power was otherwise normal. When the arms were used or held outstretched, sudden involuntary jerks were noticed in all the fingers and to a lesser extent in the proximal muscle groups.

In addition there was a moderate cerebellar ataxia of all four limbs. The deep reflexes were difficult to obtain and the biceps-jerks were absent. The abdominal reflexes were preserved and the plantar responses flexor. There was no abnormality in the sensory system.

Her gait was variable, at times relatively normal, at others it was wildly ataxic. General examination was negative except for a blood pressure of 160/100 mg.Hg.

Observations on the myoclonus.—No involuntary jerks were detected when the patient lay at rest, during the times of going to sleep, awakening or during deep sleep. When the patient was speaking, grimacing or eating, multiple small muscular twitches were seen to involve the lower face, lips and tongue. These were so pronounced at times that her lower denture was displaced and phonation was arrested.

The distribution of the jerks in the upper limbs was mainly peripheral and especially involved the fingers causing sudden flexion or extension. To a lesser extent the biceps, deltoids and trapezii were involved and in the lower limbs the quadriceps, hamstrings and hip flexors, though contraction of these muscles did not displace the limbs. The jerks were asynchronous, asynergic and arrhythmic and varied in severity from day to day but this could not be related to the time of day or to the environment.

The myoclonus was only observed in muscles which were contracting and was most noticeable if a posture was sustained or a movement was performed rapidly. Passive muscle stretch, repetitive pin-prick and thermal stimuli failed to provoke the involuntary jerks.

Investigations.—X-ray of chest and skull were normal. Electroencephalogram (report by Dr. W. A. Cobb): The EEG is a mixture of alpha rhythm at about 8 c/s and occasional theta waves with a periodicity of about half a second. Overbreathing causes a moderate and prolonged increase in the slow activity which is generalized. This is an abnormal EEG but without evidence of a focal lesion and without characteristics which are definitely epileptic.

The blood Wassermann reaction was negative. Serum proteins: total 7·1 grammes/100 ml., albumen 3·7 grammes, globulin 1·2 grammes.

Progress.—She remained in hospital till 3.11.52, when she was transferred to a convalescent home. Whilst there she had a simple fall and became mentally disturbed and negativistic. She was readmitted to hospital 27.11.52.

On admission she was found to have developed a rhythmic tremor of the small muscles of both hands and had become demented. She made a slow improvement, but for a period of three days was mentally confused. She was discharged fully orientated but with little change in her general condition.

She died 31.1.53 quite suddenly and permission for examination of the brain only was given; the spinal cord was therefore not removed.

Post mortem (report by Dr. W. G. P. Mair).—The skull cap was of average thickness. The dura mater was not unduly adherent to it. The cerebral convolutions were flattened and the sulci shallow. There was little cerebrospinal fluid in the cisterns. A well-marked pressure cone was present on the under-surface of the cerebellum. A mild degree of hippocampal herniation was also seen on either side, but more marked on the left. The cerebral hemispheres weighed 1,188 grammes; and the cerebellum and brain-stem 168 grammes.

On coronal section of the brain a small recent hæmorrhage was found in the wall of the third ventricle on the right side, involving the inferior part of the anterior pillar of the fornix and the tissue immediately below it. No obvious lesion was seen in the brain-stem or cerebellum.

Histological examination of the frontal lobes, basal ganglia, brain-stem, cerebellum and first cervical segment of the spinal cord did not show any abnormality.

Comment.—This patient had myoclonus, cerebellar ataxia and dementia and subsequently developed rhythmic tremor of the hands. She died quite suddenly and apart from recent pressure cone and a small hæmorrhage in the region of the anterior pillar of the fornix there was no macroscopic or microscopic lesion in the brain. Although a full post-mortem examination was not performed this case shows that myoclonus can occur in the absence of structural changes in the cerebellum.

Case 3 (*No.* 43791).—*C. H., baby girl, aged* 4.

The patient was admitted 27.2.53 under the care of Dr. Denis Williams.

The history was obtained from the father and mother.

When the mother was carrying the child her pregnancy was normal and uncomplicated. Parturition lasted one and a half hours and delivery was effected without instruments. Her birth weight was 7 lb. and there was no undue moulding of the head, neonatal jaundice or asphyxia. She was vaccinated and immunized between the third and fourth months without any complication and passed her milestones at the appropriate times. At the age of 2 years she had measles and at 4 a right-sided aural discharge which resolved within a few days. Up to the time of her present illness she was considered to be a normal child.

Her parents were healthy and unrelated to one another. Both were rhesus-positive and their Wassermann reactions were negative. They have an elder daughter aged 8 who has bilateral cataract which was diagnosed at the age of

1 year. The mother's and the father's families were unaffected by neurological disease or skeletal deformity.

The patient's illness commenced in February 1952 when she had a convulsion. Without warning she fell to the ground unconscious, her face pale, her eyes open and staring. Clonic movements of the jaw were noticed but the limbs remained immobile. Within a few seconds her whole body became stiff with extension of the limbs. She came to herself within about two minutes.

Since that time her fits recurred every fourteen to twenty-one days at any time of the day or night and no predisposing or precipitating factors were recognized. From the onset of these attacks she became mentally dull and dirty in her habits but there was no evidence of destructiveness or tantrums.

About one month later she started to have blank spells in which she remained standing, but was unaware of her surroundings, for 30–60 seconds. These recurred twenty to thirty times a day.

In January 1953 her gait became unsteady. The degree of ataxia varied from day to day and was due to sudden involuntary jerks of her right leg which threw her off balance. These also occurred when she was standing but were never observed at rest or during sleep. No predisposing or precipitating factors were recognized though the involuntary jerks were most severe in the early morning.

All her symptoms were progressive, so that by the time of admission, the jerks recurred every few minutes, she was mentally backward and took little interest in her surroundings.

On examination she was a pale child with flaxen hair, weighing 2 st. 6 lb. She did not play with her toys and was unable to feed or dress herself. She obeyed forceful commands but it was difficult to hold her attention owing to frequent attacks of *petit mal*. Her vocabulary was average for her age and, though she did not speak spontaneously, speech was normal. It proved impossible to teach her the names of objects previously unfamiliar to her.

There was a fine side-to-side titubation of the head, which was slightly rotated and inclined to the right. The skull circumference was 19 in. and the fontanelles were closed. There was a high palatal arch, the fingers were tapering and the little fingers on either side only reached the level of the first interphalangeal joint of the ring finger. No other developmental abnormality was detected.

Vision and hearing were normal, and, with the exception of a few unsustained nystagmoid jerks in extreme lateral conjugate gaze, the cranial nerves were intact.

Development, power and tone were normal. Movements of the limbs revealed a slight but definite ataxia most pronounced upon the right side. The deep tendon reflexes were difficult to obtain and the ankle-jerks absent. The abdominal reflexes were preserved and the plantar responses flexor.

When placed on her feet she stood on a wide base but there was no Rombergism. Gait was slightly ataxic, but in addition there were sudden involuntary jerks of the right leg which threw her temporarily off balance.

In the sensory system pin-prick, touch and vibration were appreciated over all areas. General examination revealed no other abnormality.

Observations on the myoclonus.—When the patient was awake the myoclonus was confined to the right leg. It was not present during relaxation or non-weight-bearing movements and only appeared when she stood or walked. The involuntary jerks were synchronous and arrhythmic, involving the quadriceps and gluteal muscles, causing sudden flexion, abduction and external rotation at the hip. They were most readily provoked if a movement was performed rapidly, by a sudden change of posture, or if maximal power was exerted. Startle, passive muscle stretch, repetitive pin-prick and thermal stimuli failed to provoke the myoclonus.

While she was falling asleep the lower facial muscles, trapezius, deltoid, triceps, biceps, glutei and quadriceps of both sides became involved in spontaneous small

contractions. These were arrhythmic and asynchronous and though there was slight displacement of the face and arms the legs were not moved. The jerks disappeared during deep sleep but reappeared shortly before she awoke.

On one occasion these small contractions commenced during light sleep and over a period of five minutes increased in magnitude, extent and distribution till they terminated in a convulsion which lasted two to three minutes. After the fit, walking and standing were not interrupted by the myoclonus for the subsequent two hours.

Investigations.—X-rays of chest, skull and lumbar spine were normal. The erythrocyte sedimentation rate was 3 mm./hour (Wintrobe) and a full blood count was normal. Blood chemistry showed the following: total protein 7·36 grammes/100 ml; globulin 1·16, albumen 4·64. Total cholesterol 162·5 mg./100 ml.; free cholesterol 46·9, lipid phosphorus 9·85, total phospho-lipid phosphorus 246·25; lecithin 141·8. The urine showed no abnormal constituents. Cerebrospinal fluid was clear and colourless; cells 3 lymphocytes, protein 40 mg., Lange no change. The Wassermann reactions of the blood and cerebrospinal fluid were negative. Electroencephalogram (report by Dr. W. A. Cobb): The general amplitude of the EEG is high and it is difficult to be sure whether there is any normal activity at all. There is a wide range of slow rhythms in which 2 c/s activity predominates, tending to occur in fairly regular runs which are sometimes symmetrical and sometimes predominantly on one side or the other. In addition there are a fairly large number of spikes and sharp waves occurring in all areas in a random manner, with no constant relationship to the slow activity. It is doubtful if opening the eyes causes any change.

Flicker stimulation shows no clear response at most frequencies but, at about 13 c/s, there is a generalized response during which the spike activity seems to increase and the child is distressed and tries to draw away from the light.

This is a severely abnormal EEG of a kind which is associated with generalized degenerative diseases in children.

Ventriculogram (report by Dr. H. Davies): Good filling of the ventricular system was obtained. The septum pellucidum and the third ventricle lay in the mid-line. The third and lateral ventricles were normal in size, shape and position. A very incomplete filling of the fourth ventricle was obtained and the aqueduct was not seen. The fourth ventricle lay in the mid-line and a moderately large cisterna magna was demonstrated. Quite a considerable quantity of air entered the supratentorial subdural space but I do not regard this as being of significance.

Conclusion.—No supratentorial lesion is detected. A better assessment of the fourth ventricle and filling of the aqueduct could be obtained by lumbar encephalogram. I think it is quite possible that the fourth ventricle is considerably enlarged.

Brain biopsy from the right parietal region (report by Dr. W. Blackwood): Sections show leptomeninges and cortex in which there is no evidence of lipidoses or any other abnormality.

Progress.—During the following sixteen days the patient's condition steadily deteriorated. The myoclonus became more extensive and involved the left leg, extensors of the spine and neck. Within a few seconds of rising to her feet she was thrown to the ground by the jerks. Her periods of absence recurred every few minutes and could not be controlled by chloral hydrate, phenobarbitone or tridione. During the day she was apathetic and at night was restless and screamed.

She was given phenurone (phenyl-acetyl-urea) 0·25 gramme three times a day. Within three days a marked change was observed. The myoclonus became less severe and was limited once more to the right leg and she was able to walk fairly well. She became brighter mentally, played with her toys and was able to converse normally whilst her periods of absence diminished to a frequency of about five per day.

Comment.—This patient had mental deterioration, epilepsy, myoclonus and a minimal cerebellar ataxia. The symptoms started at the age of 3 and were steadily progressive. Investigations did not support a diagnosis of a lipidosis and the underlying pathology remains obscure. The response to phenurone has been dramatic but it is too early to tell whether this improvement will be maintained.

Case 4 (*No.* 8547).—*A. B., male aged* 18 (*unemployed*).

The patient was admitted 4.3.53 under the care of Dr. E. A. Carmichael.

The parents of the patient were first cousins. Both were rhesus-positive and had negative blood Wassermann reactions. The paternal grandfather died at the age of 44 from general paralysis of the insane but the family history was otherwise irrelevant. The patient was an only child. The maternal pregnancy was normal and uncomplicated. Birth lasted seven and a half hours and was effected without instruments. The birth weight was 7 lb. and there was no evidence of excessive moulding of the head, neonatal asphyxia or jaundice. He passed his milestones at the appropriate times, and apart from the common exanthemata, remained in good health up to his present illness.

From the age of 12 he was first noticed to be rather clumsy with his hands and is said to have had several falls. Aged 13 he had his first major convulsion and was reported to have been unconscious for one hour with twitching of the face and arms. Shortly after this he became aware of sudden involuntary jerks of both arms which only occurred in the early mornings and wore off in the subsequent two hours. These gradually became more persistent so that by the end of six months they occurred during the whole day. On account of these his handwriting became a scribble and his gait unsteady. He was afraid to go out by himself and came down the stairs on his seat one step at a time. After a second generalized fit he was admitted to hospital 14.9.49.

On examination he was of average intelligence, speech, the special senses, cranial nerves and sensation were normal. Alternating movements of the limbs were initially well performed, but, with continued action, became irregular and interrupted by involuntary jerks. If he turned round suddenly similar jerks involved his lower limbs, and he fell down. The deep reflexes were normal and the plantar responses flexor.

Cerebrospinal fluid was clear and colourless, containing no cells and 30 mg./100 of protein; Lange no change. Air encephalography was normal. The EEG showed numerous spikes in both classical and larval forms; fast activity was detected in the fronto-temporal regions and the alpha rhythm was absent.

He was discharged from hospital 2.10.49 and given phenobarbitone $\frac{1}{2}$ grain and epanutin $1\frac{1}{2}$ grains three times a day.

In January 1952 he was readmitted. No additional physical signs were recorded. After a trial with tridione, mysoline and sodium amytal it was appreciated that his jerks were best controlled by phenurone 0·5 gramme four times a day and phenobarbitone $\frac{1}{2}$ grain mane and $\frac{3}{4}$ grain nocte. He was discharged 31.1.52.

Since that time he has had six major convulsions, all of which occurred within an hour of waking and followed an exacerbation of his involuntary jerks. After the fits he was symptom-free for the remainder of the day. The jerks themselves only occurred when he was performing a movement or maintaining a posture. Sometimes his speech was affected when it became irregular and was accompanied by twitching of the lips and tongue.

On examination he was a highly intelligent patient of average development. Speaking was accompanied by rapid irregular twitchings of the lower facial muscles and tongue which at times interrupted vocalization. Similar muscle twitches

involved the eyelids when they were lightly closed and, if they were screwed up in a maximal contraction, the orbicularis oculi and upper facial muscles were affected. In extreme lateral gaze irregular nystagmoid jerks were observed, but within the limits of binocular vision there was no nystagmus. The soft palate was involved in similar arrhythmic jerks but these disappeared when the tongue was protruded or during phonation.

No other abnormality was detected in the cranial nerves and the special senses and sensory system were normal.

There was a moderate cerebellar inco-ordination with a terminal action tremor of both arms and in addition during movement sudden involuntary jerks involved those muscles which were contracting. The tendon reflexes were brisk and equal, the abdominal reflexes preserved and the plantar responses flexor. Power, tone and general examination were normal; the blood pressure was 140/90 mg.Hg.

Observations on the myoclonus.—No involuntary jerks were seen during complete relaxation, in the period of falling asleep, waking up or during deep sleep. The jerks were only observed in those muscles which were in a state of contraction whilst the patient was awake. With the exception of the diaphragm and the intrinsic muscles of the larynx, every voluntary muscle which could be observed clinically was affected. Voluntary movement always provoked the jerks but they also occurred during yawning, laughing and changes of posture.

The magnitude of the jerks varied from day to day and from hour to hour but they were always most severe in the two-hour period after waking. Apart from this their severity was proportional to the power of voluntary contraction. For instance, elbow flexion was accompanied by a few irregular twitches confined to the biceps. If the resistance to this movement was increased the distribution of the jerks spread to involve synergists and fixators, and during maximal effort the muscles of the face, neck, shoulder, trunk and legs were also involved. The magnitude of this jerk was also greater in the individual muscles at this time than during a minimal voluntary contraction. Other factors increasing the severity of the jerks included a change in the direction of a movement, acceleration or deceleration of a movement in one direction and a sustained contraction. During periods of anxiety the jerks tended to be of greater amplitude but no other predisposing factors could be identified.

As a result of the myoclonus, his gait was jerky and unsteady and this disorder was accentuated by asking the patient to run or suddenly turn round when, on his bad days, he fell down.

The following sensory stimuli failed to elicit a jerk when the patient lay at rest: repetitive pin-prick, passive muscle stretch, thermal stimuli, distension of the stomach with 1 litre of water, distension of the bladder with 24 ounces of urine (at this time dull pain was experienced) and repetitive acoustic stimuli at 700, 800 and 900 decibels at 100–1,000 c/s.

Unexpected loud noises which produced a change of posture were followed by a single synchronous jerk.

An attempt was made to discover whether the morning exacerbation of the condition was correlated with acidosis, alkalosis or hypoglycæmia. Administration of 75 grains of ammonium chloride over a period of twelve hours did not modify this pattern, and hyperventilation performed for periods of two minutes was not accompanied by any change in the magnitude or frequency of the jerks. Blood-sugar levels taken at half-hourly intervals after waking could not be related to the improvement nor was this hastened by the administration of 50 grammes of glucose by mouth. Relaxation for six hours without sleep, under equivalent conditions, was not followed by the exacerbation noticed after nocturnal sleep. Furthermore, sleep induced with 6 grains of sodium amytal during the daytime was not followed by an increase of the myoclonus.

An attempt was made to deafferentate the left leg by placing a pneumatic cuff round the thigh and inflating it to a pressure of 200 mm.Hg. After twenty-five minutes the patient was unable to appreciate movement at the left ankle. He was instructed to dorsiflex both ankles under visual control. This movement was accompanied by irregular muscle jerks, which were asynchronous, and involved the dorsiflexors of both ankles. These did not differ in any essential quality between the two sides. Within three minutes power at the left ankle failed and with this the jerks disappeared on that side.

The evening dose of phenurone was then omitted. During the night the patient was restless and was unable to get out of bed owing to the severity of the jerks which were generalized and accompanied the slightest attempt to move. The next morning at 5.30 a.m. massive jerks were observed and during one of these the patient was thrown off his bed on to the floor. He was unable to rise unassisted and his speech was almost unintelligible. 1 gramme of phenurone was administered orally and the myoclonus gradually became less marked in the succeeding hour, returning to the average for a bad day after three hours.

Optokinetic nystagmus was normal at the three test speeds of the rotating drum to the left and right. Caloric responses were normal. Electroencephalogram (report by Dr. W. A. Cobb): In the frontal regions spreading fairly far back there is a continuous, moderate voltage, fast rhythm while posteriorly a rhythm from 5–7 c/s is almost continuous. The latter has the distribution and behaviour of alpha rhythm and no clear alpha rhythm of normal frequency can be seen. Many scattered small spikes occur sometimes with a constant generalized brief episode of high voltage 2–3 c/s waves usually mixed with spikes. Overbreathing has slight effect. Flicker stimulation possibly causes some increase in the spikes associated with the theta rhythm in the occipital regions; it probably also causes a more generalized disturbance, but this is difficult to be certain because the patient showed an intense aversion to flicker and invariably turned away from the light, resulting in muscle artefacts. There seem at this time to be also an increase in the myoclonic jerks.

There has been over a period of nearly five years very little essential change in the EEG which has always shown a predominant background of theta rhythm with episodes of slow waves and spikes, the character of which vary little from record to record.

Comment.—An only child of consanguineous parents who was normal up to the age of 12 when he developed a mild cerebellar ataxia. Shortly afterwards he started to have occasional generalized convulsions and persistent action myoclonus. Investigations did not help to determine the underlying pathology. The myoclonus was partially controlled by phenurone.

Case 5 (*No.* 44008).—*V. T., boy aged* 3 *years.*

The patient was admitted to hospital 30.3.53, under the care of Dr. William Gooddy.

The history was obtained from the parents and from perusal of previous hospital records.

The father was rhesus-positive, the mother rhesus-negative: their Wassermann reactions were negative. During the early months of the pregnancy, the mother felt unusually tired and noticed a rapid increase in her abdominal girth. She was admitted to hospital during the sixth month as an acute emergency when a ruptured ovarian cyst was removed. Recovery was complete within five weeks but was complicated by a post-operative pneumonia for which she received penicillin. The

child was born at full term and delivery was effected in hospital after six and a half hours without instruments. The birth-weight was 7 lb. 4 oz. and there was no undue moulding of the head or neonatal asphyxia.

Blood was taken from the mother and from the umbilical cord but no rhesus antibodies were detected, and Coombs test was negative. From the fourth to the seventh day a mild jaundice was noticed. The child did not accept the breast and was bottle fed. He was an only child and none of his family suffered from nervous or mental disease.

According to the mother he remained well up to the age of 4 months but was never able to hold his head up. At this time he was vaccinated. The first two attempts were unsuccessful, but, four days after the third scarification, he developed fever, twitching of the face and arms and was unable to retain his feeds. He was admitted to hospital where he was found to be blind, deaf and mentally deficient. He was discharged after two weeks and his mother noticed that he took little interest in his surroundings and had occasional fits in which he lost consciousness and his arms and legs stiffened for two minutes at a time. He never achieved sphincter control, swallowing was impaired and he was difficult to feed.

In August 1950 he was reported to have primary optic atrophy with inactive pupils and "technical blindness."

During the next year he was seen by many specialists at different hospitals who all confirmed that the child suffered from epilepsy with mental deficiency, blindness and deafness.

In May 1951 he was admitted to a hospital with diarrhœa and vomiting and bronchitis. In addition to the previous physical signs there were continuous rolling of the eyes and chewing movements of the lower jaw. Deep reflexes were brisk, more so on the right, and the plantar responses were extensor. X-rays of the chest and skull and full blood examinations are reported to have been normal. Since that time his tonic fits have recurred on average once every two weeks and occasional jerks of the arms and legs have been seen.

On examination he was a well-nourished child of average development. He lay on his back with his upper limbs flexed at the elbows and adducted at the shoulders with his forearms slightly pronated and his fists clenched. Both lower limbs were extended and the feet in equinovarus. His head was slightly retracted and rotated though a few degrees to the left. Apart from the presence of small epicanthic folds no abnormality was detected on general examination. He was unable to hold up his head, sit up or talk.

The skull circumference was 19½ in. and the vault was slightly flattened on the left-hand side; the fontanelles were closed. There was no reaction to loud noise or to moving objects with any quadrant of the visual fields. Ophthalmoscopy revealed flat pale discs, sharply defined with narrowed vessels.

The pupils were equal and regular but reacted sluggishly to light over a very small range. Continuous rolling movements of the globes were observed and there was a tendency for them to be drawn upwards and to the left. At such times the visual axes were not always parallel. Facial movements when he cried were equal and at other times when chewing movements of the jaw were seen. During these movements there were occasional sudden muscular twitches of the left or right angle of the mouth. The cranial nerves appeared to be otherwise normal.

The limbs were seldom moved spontaneously but were withdrawn promptly from noxious stimuli. Attempts to displace the limbs showed a marked spasticity of pyramidal distribution. Rotation of the occiput to either side was accompanied by a slight diminution of flexor tone and a relative increase of extensor tone on the opposite side. The deep reflexes were all very brisk, the abdominal reflexes preserved and the plantar responses feebly extensor.

Observations on the myoclonus.—Occasional sudden involuntary jerks were

observed in one or more of the following muscles: the facial muscles, particularly around the mouth, the sternomastoids, trapezii, biceps and triceps, extensors of the spine, quadriceps and gastrocnemius of both sides. These were irregular in amplitude and arrhythmic in character.

The jerks were infrequent in appearance and on some occasions were not seen for as long as two hours at a time. When several muscle groups were involved they were synchronous and assynergic and produced considerable displacement of the limbs. The distal muscles were not affected. They occurred equally at rest or during the occasional spontaneous movements that were observed, but were not seen while falling asleep, in deep sleep or on waking. Passive muscle stretch, repetitive pin-prick and thermal stimuli did not provoke the jerks.

Investigations.—X-rays of skull (report by Dr. J. L. G. Thomson): There is considerable asymmetry of the skull vault, the left side being very markedly flatter and smaller. X-rays of chest and lumbar spine were normal. A full blood count was normal. Wassermann reaction was negative. The blood group A, rhesus positive. Electrophoresis of the serum revealed no abnormal protein patterns. Blood lipid phosphorus 107 mg./100 ml., total phospholipid phosphorus 267·6 mg./100 ml. Cerebrospinal fluid was obtained by ventricular tap and contained 1,200 red cells/c.mm., protein 20 mg./100, Pandy and Wassermann reactions negative. Toxoplasma dye and complement-fixation tests negative.

Electroencephalogram (report by Dr. W. A. Cobb): The EEG consists almost entirely of high voltage slow activity from 1 c/s upwards; much of this is irregular, but there are also regular runs of 2 c/s and 4-5 c/s waves. This slow activity is bilateral but possibly a little larger on the left. There are also frequent single sharp waves which are present on both sides. This is a grossly abnormal and complex EEG, showing a universal disturbance, possibly greatest on the left side.

Ventriculogram (report by Dr. H. Davies): The right cerebral hemisphere is collapsed and a considerable quantity of subdural air is present over it. The brain tissue can be seen to be only a few millimetres thick and the underlying ventricle is obviously very large. The left lateral ventricle is also enormous, but a little cerebral tissue is spared superiorly in front. The third ventricle, as much as can be seen of it, appears to be much more normal in size and is central. The fourth ventricle is a little large but not unduly so and the cisterna magna is also a little capacious. The pontine cistern is filled and is normal. Some air has also reached the cortical sulci and these are enlarged. *Conclusions.*—The appearances suggest very gross atrophy of the cerebral hemispheres. The basal ganglia region, however, would appear to be more normal. The cerebellum is a little atrophic.

Brain biopsy (report by Dr. W. Blackwood).—The material consisted of several tiny fragments of cortex only. No obvious nerve cell changes have been seen and there is no increase of the microglia or astrocytes.

Comment.—The inability to breast-feed, difficulty in swallowing and failure to hold the head up suggested that the child had been abnormal since birth or early neonatal life. In the absence of a history of birth trauma the asymmetry of the skull suggested a congenital defect. This may have been due to operative interference during the mother's pregnancy; to the administration of a general anæsthetic; or to the post-operative pneumonia which was treated with antibiotics. This case is of particular interest since myoclonus was observed in the presence of decerebrate rigidity.

Case 6 (*No.* 44717).—*C. D., male aged* 39 (*a crane driver*).

This patient was admitted to Guy's Hospital in May 1952 and a report (Case 5) is included in a paper by Sir Charles Symonds entitled "Nocturnal Myoclonus" (*J. Neurol. Psychiat.* (1953) **16**, 166). He was subsequently admitted to The National Hospital, Queen Square, 19.4.53, where the following study was made.

The patient was married and had two healthy children. There was no family history of neurological disease or skeletal deformity. At the ages of 24 and 28 he had two accidents of an identical character in which a detonator exploded and threw him a distance of 20 feet on to his back. He did not strike his head or lose consciousness but on the second occasion fractured his right ankle. He had influenzal pneumonia at the age of 26. From childhood he had been liable to faint at the sight of blood and under conditions of mental stress. Also if he rose quickly from the recumbent position or stood for long periods he felt faint and complained of sweating, blurred vision and weakness of the legs. These symptoms disappeared within a few minutes if he sat down but, if he remained standing, he lost consciousness for three to ten minutes and when he came to himself felt giddy for about a quarter of an hour. On four occasions, however, since 1938 he had suddenly lost consciousness whilst sitting down for periods of up to half an hour and had amnesia of one to two hours when he regained consciousness. He never bit his tongue or passed urine and was not seen to have convulsions.

His present symptoms started in November 1951 when he noticed involuntary jerks of his left lower limb at about 11 p.m. whilst lying in bed talking to his wife. These caused flexion at the hip and knee and recurred at irregular intervals for some ten minutes. This symptom recurred every subsequent night and by the end of a month his right lower limb was also affected. By the end of two months his upper limbs were involved, the attacks causing them suddenly to extend at the elbow so violently that on several occasions he struck his wife. Within three months the trunk was also affected, with attacks of sudden extension of the spine. Since that time the distribution has not altered and the face and neck have been spared; speech and respiration have never been interrupted by the jerks. The duration of the attacks gradually increased till they persisted for up to four hours at a time and recurred several times each night. His wife stated that they continued during sleep but were less pronounced.

Until one year ago no diurnal jerks occurred and the jerks only commenced at night when he lay down, and disappeared if he got up and walked about. Six months before admission they also occurred if he was fully relaxed in a chair or at the cinema during the day. He had his good and his bad nights but these could not be related to fatigue, the consumption of alcohol, tea or coffee or to emotional stress. In his attacks there was no disturbance of consciousness nor did he have pain or paræsthesiæ.

May 1952 he was admitted to Guy's Hospital with anorexia, loss of weight and dull epigastric pain. Full investigation, including barium meal and gastroscopy, was negative. In December 1952 he was readmitted to the same hospital. The cerebrospinal fluid was clear and colourless containing 1 lymphocyte/c.mm., 20 mg. per cent protein, 50 mg. per cent sugar. Lange no change. He was given two capsules of tridione every night half an hour before retiring and this effected a considerable improvement. The jerks became less severe and recurred on average two to three times a week for a few minutes each night. Within two months, however, in spite of continued medication he relapsed to his former state and was unable to do a full day's work because of insufficient sleep.

On examination he was of average development and intelligence. No abnormality was found in the special senses, cranial nerves, motor or sensory systems. General examination was normal; the blood pressure 150/85mm.Hg. No involuntary movements were detected either at rest or during activity.

17.4.53, at 5 p.m., he was re-examined in a position of complete relaxation and no abnormality was detected. Passive muscle stretch, repetitive pin-prick and thermal stimuli failed to provoke the jerks. Hyperventilation for two minutes and rebreathing from a paper bag for half an hour were also ineffective.

19.4.53, at 9 p.m., he was examined again in a state of complete relaxation. After six minutes he had a feeling of tightness in his left lower limb and at the same time involuntary jerks were seen in it. Within four minutes the right lower limb was affected and within six minutes the right upper limb was involved. The left upper limb, face and neck were spared.

The following muscles were involved: Right upper limb—rhomboids and medial scapular group, trapezius, supraspinatus, latissimus dorsi, pectoralis major, deltoid, biceps, coracobrachialis and triceps. The trunk—erector spinæ, the abdominal obliques and recti abdominis. Lower limbs—pectineus, glutei, adductors, quadriceps, ham strings and gastrocnemii.

The jerks consisted of: Right upper limb—forward flexion and elevation of the right shoulder and extension or flexion of the elbow. The trunk—occasional slight extension of the back. The lower limbs—flexion at the knees and hips.

There was no particular rhythm or sequence. When a limb was affected all muscle groups at each joint appeared to contract synchronously. The resultant movement was very sudden and brief. Jerks in the two lower limbs, or in an upper and a lower limb, occurred asynchronously, with the exception of the trunk muscles which tended to coincide with contractions of one or other lower limb.

Inspection of the lower limbs, abdomen and buttocks revealed the presence of very rapid irregular twitchings of the muscles listed above. Different portions of the muscles were involved at different moments at rates of about 100–150/minute. Superimposed upon this were the jerks previously described and these supervened every 6–20 seconds and immediately followed an increase in the magnitude of the muscular twitchings.

In the upper limbs no such twitchings were observed and palpation failed to detect their presence. The large jerks were less frequent than in the lower limbs. Over the trunk similar muscular twitchings were observed but at a slower rate averaging 50–80/minute.

Repetitive tendon or muscle percussion performed over the right biceps, where the jerks were most infrequent, resulted in the constant appearance of a large involuntary jerk similar to that previously described. This was at first confined to the right upper limb, but, if stimulation was continued, spread to involve the right lower limb and later the left. Percussion of the left upper limb was ineffective.

Arterial occlusion of either the right upper limb or either lower limb for twenty minutes did not modify the pattern of the spontaneous voluntary movements.

After about one hour the jerks became more infrequent and disappeared in the right upper limb. In the lower limbs the muscular twitches persisted but produced no motor effect. The large jerks diminished in amplitude and frequency till after ten minutes no motor effect was observed.

Tendon and muscle percussion over the left quadriceps applied at this time caused a reappearance of the jerks, at first in the left lower limb, but within two minutes the right lower limb and after a further four minutes the right upper limb. After a total of one and a half hours all contractions ceased.

Subsequent observations demonstrated that the left upper limb was occasionally involved. Voluntary movements of the limbs involved by the jerks, abolished the myoclonus and if the patient walked about for two minutes all the involuntary jerks disappeared.

Investigations.—Blood Wassermann negative. Erythrocyte sedimentation rate 13 mm./27 mm. (Wintrobe). Hæmoglobin 13·3 grammes/100 ml. Total white cells 7,400 with a normal differential count. X-rays of skull and lumbar spine

were normal. X-ray of chest revealed a small calcified primary focus in the left mid-zone.

Electroencephalogram (reports by Dr. W. Cobb).—23.4.53: The record was at first very flat but, as the patient drowsed following 4½ grains of seconal, it became more active and then went through the stages of light sleep. No myoclonus occurred during drowsiness and the EEG shows nothing asymmetrical or otherwise abnormal.

The EEG was recorded 24.4.53 between 10 and 11 p.m. when the patient was alert and co-operative but nevertheless had numerous myoclonic jerks, mainly of the legs. The EEG was as reported yesterday (23.4.53) but corresponding with most of the jerks there were brief outbursts of slow waves; these are rather inconstant in form and distribution and in some cases are certainly, and in others most probably, artefacts; there is nothing which can with absolute certainty be said to correspond in the cerebral electrical activity with the motor outbursts.

Progress.—The patient was given phenobarbitone ½ grain and phenurone 0·5 gramme three times a day. Over the following three days the myoclonus remained unaltered but on the third night the patient was completely free from the jerks. Since that time he has remained almost symptom-free apart from occasional periods of up to ten minutes prior to falling asleep.

Comment.—This patient had myoclonus which only appeared during relaxation, and occasional fits. There were no other physical signs and, under suitable conditions, passive muscle stretch provoked the involuntary jerks. The clinical picture closely resembled that of paramyoclonus multiplex though, unlike that condition, the jerks caused displacement of the limbs. The myoclonus was partially controlled by tridione but the patient relapsed after two months. The response to phenurone was dramatic but full assessment of the value of this treatment is not yet possible.

Discussion and Conclusions

Myoclonus as an isolated phenomenon.—It has been argued that the term "Essential myoclonus" should be reserved for transient or persistent myoclonus which is not accompanied by other neurological signs. The apparent absence of a structural pathology in this condition should cause no surprise in view of the work of Gastaut and Roger (1951). Utilizing a combination of cardiazole and flicker they showed that it was possible to provoke myoclonus in normal subjects.

One case (6) of essential myoclonus is presented. The involuntary jerks were only seen during muscular relaxation and consisted of diffuse asynchronous small contractions that gave rise to larger jerks which displaced the limbs. Immediately after their cessation repetitive passive muscle stretch caused them to reappear in the limb that was being stimulated. If this stimulation was long continued the myoclonus spread to involve other segments, at first on the ipsilateral but later on the contralateral side. Other forms of stimulation were ineffective and the myoclonus was abolished by voluntary movement.

These findings suggest that during relaxation an excitatory state is set up involving neurones of the reflex arc concerned with muscle stretch.

This was considered to be at a spinal level since muscles innervated by cranial nerves were not involved and the spread, which followed stimulation, did not follow a cortical march. Since voluntary movement inhibited the myoclonus it is unlikely that the anterior horn cells were primarily affected but rather the intercalated neurones within the dorsal horn. It is possible that, in essential myoclonus, physiological afferent impulses provide a sufficient stimulus to provoke the involuntary jerks.

Myoclonus in relation to epilepsy.—The relation of myoclonus to epilepsy is stressed by the frequent occurrence of one or both conditions in several members of a family and by the common concurrence of the two maladies in one patient. Probably 60 per cent of epileptics have occasional myoclonus and, whilst persistent myoclonus is rare, yet the greater number also have convulsions.

The sequence of involuntary jerks which lead up to a fit, which has been described by others, was observed in Case 3. The myoclonus commenced during light sleep, gradually increasing in magnitude, frequency and extent until the patient was convulsed. After the fit no myoclonus was seen for several hours. Patient No. 4 gave a history of similar attacks but was not studied during one.

These findings recall the experimental work of Muskens (1928) who subjected cats to intoxication with camphor. With increasing dosages he obtained, first reflex myoclonus following tactile stimulation, then spontaneous myoclonus of increasing severity, and finally convulsions. During the post-ictal period neither reflex nor spontaneous myoclonus was detected.

In addition to these considerations both myoclonus and epilepsy can be provoked in normal people by a combination of analeptic drugs and flicker stimulation.

Myoclonus as a symptom of organic disease.—The greater proportion of cases with persistent myoclonus have physical signs which bear witness to structural changes in the central nervous system. The regions implicated in order of frequency are the cerebellum or its connexions, the pyramidal and extrapyramidal systems, and the cerebral cortex. In the latter instance there may be dementia.

The distribution of physical signs in this series is shown in the table.

Case No.	1	2	3	4	5	6
Cerebellar ..	+	+	+	+	0	0
Pyramidal ..	0	0	0	0	+	0
Extrapyramidal	+	+	0	0	+	0
Mental changes	0	+	+	0	+	0

It may be difficult to determine whether apparent dementia is due to structural disease or to recurrent interference with consciousness. Mental deterioration was present in Cases 3 and 5 and in both the EEG suggested widespread degenerative changes of the cerebral cortex. This contention was confirmed in Case 5, but in Case 3 air studies failed to

demonstrate a supratentorial lesion. This patient was given phenurone, which reduced the number of fits, and the mental state improved.

Pathology.—No pathology is peculiar to myoclonus, a physical sign common to many diseases. Van Bogaert and others (1950) have shown that myoclonus is most frequently associated with cerebellar degenerations and heredo-familial ataxias and 4 patients (1, 2, 3 and 4) showed the clinical features of a cerebellar degeneration. A fuller understanding of the underlying pathology was not achieved by laboratory investigations and in Cases 3 and 5 the blood chemistry did not indicate a disturbance of lipid metabolism. The possibility that the disorders were genetically determined was suggested in Case 1 by the family history, and in Case 4 by parental consanguinity.

Patient No. 5 had been unable to feed from the breast and did not hold his head up by the fourth month. In the absence of a history of birth trauma, the gross abnormality of the cerebral hemispheres together with asymmetry of the skull were considered to be due to a developmental defect, probably arising in connexion with the ruptured ovarian cyst, the operative interference or the post-operative complications during the sixth month of the maternal pregnancy.

Patient No. 2 died and at autopsy no unequivocal macroscopic or microscopic lesion was found in the brain or first cervical segment of the cord; in particular the region of the dentate nucleus and the cerebellum were normal. During life this patient had exhibited myoclonus, rhythmic tremor of the hands, ataxia and dementia, so it is probable that the histological techniques which are at present available were insufficiently refined to demonstrate the underlying disturbance of neuronal function. The negative findings show, however, that a gross structural abnormality of the dentate nucleus is not essential for the production of myoclonus.

Many previous writers have stressed the frequency with which this region has been involved and some (Hodskins and Yakovlev, 1930) have been tempted to suggest that myoclonus depends for its production on the interruption of cerebello-fugal pathways. Though this may be so, it appears that there is insufficient evidence for this assertion, for, in a large number of cases, more than one lesion has been detected which renders clinico-anatomical correlation difficult. It is more likely that the high incidence of lesions of the dentate nucleus is related to the cerebellar degenerations and heredo-familial ataxias which so commonly accompany myoclonus rather than to the myoclonus itself.

Electroencephalography.—The different abnormalities which may be recorded by the EEG in patients with myoclonus have been reviewed by Gastaut and Rémond (1952). They concluded that these could best be explained on the basis of a discharging lesion, deeply and centrally placed, which activated both cerebral hemispheres.

The results in this series are in general agreement with their findings in that the abnormal complexes were bilateral and diffuse, without focal

qualities, and there was no definite correlation between the involuntary jerks and the activity registered from the scalp electrodes.

Variations in the quality of symptomatic myoclonus.—A study of symptomatic myoclonus in Cases 1, 2 and 4 showed that the involuntary jerks only involved agonist muscles which were contracting. The myoclonus was most readily provoked by a voluntary movement but was also seen during involuntary changes of posture. The size of the jerk increased proportionately with the speed at which a movement was performed and with the force exerted. It was therefore related to the rate and degree of recruitment of motor units.

These characteristics were also found in Case 3 though in addition myoclonus was observed during partial muscular relaxation.

It was concluded that there was a disturbance of neuronal activity which was confined to descending pathways. This especially involved the pyramidal tracts, though in Case 3 other neurones, probably of the extrapyramidal system, were also affected. Since muscles innervated by cranial nerves were affected by the myoclonus, this disturbance was not restricted to spinal centres.

The occurrence of myoclonus in a case (5) with decerebrate rigidity has been recorded. In addition all the patients had bilateral jerks without interference with consciousness and there was no correlation between these and the EEG findings. It is tempting to conclude that the cerebral cortex plays little or no part in the production of myoclonus.

The post-dormitial accentuation of myoclonus seen in Cases 3 and 4 was studied in Case 4. It could not be related to spontaneous or induced changes in the blood sugar level nor was it influenced by procedures calculated to alter the acid-base equilibrium. Nocturnal relaxation without sleep and diurnal sleep under sodium amytal were not followed by an increase in the severity of the myoclonus. The mechanism of this phenomenon remains obscure but is likely to be one closely associated with physiological sleep.

Treatment.—Three patients received phenurone (3, 4 and 6) and after two to three days there was a diminution in the frequency, magnitude and extent of the myoclonus. Because these patients also suffered from epilepsy they were given phenobarbitone in addition.

Patient No. 6 had shown a transient response, lasting two months, to tridione. Although this patient has been observed only for a few months the results obtained in all 3 cases suggest that a further trial with phenurone is warranted.

Summary

(1) Myoclonus is defined as "a disturbance of neuronal activity that gives rise to very sudden involuntary jerks, which are asynergic and arrhythmic, involving portions of muscles, whole muscles or muscle groups."

(2) A short review of the literature is included under the headings of "Myoclonus, without epilepsy" and "Myoclonus-epilepsy."

(3) 6 cases with myoclonus are presented together with an analysis of the involuntary movements which were observed.

(4) The relation of myoclonus to epilepsy is considered and the EEG findings briefly discussed.

(5) One case came to autopsy and no macroscopic or microscopic abnormality was detected.

(6) It was considered that in essential myoclonus an excitatory state is set up involving neurones of the spinal reflex arc concerned with muscle stretch. This may allow physiological afferent impulses to provoke involuntary jerks.

(7) In 5 cases with symptomatic myoclonus the underlying disturbance of neuronal activity was confined to descending motor pathways and was not restricted to the spinal cord.

(8) Phenurone (Phenyl-acetyl-urea) was given to 3 patients with myoclonus and this was followed by a diminution in the severity of the involuntary jerks.

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A HYPOTHESIS REGARDING THE BRAIN MODIFICATIONS UNDERLYING MEMORY

BY

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THE identification of the cortical changes associated with memory is one of the most pressing problems in the development of a theory of brain function (Eccles, 1953). Hypotheses are needed which separate the general property of memory, or change by use, from more complex processes such as adaptive learning, feed-back mechanisms, and inhibition. The hypothesis outlined here does not exclude the presence of other mechanisms and is proposed as a supplement to the established theory of neurone action. It is intended to cover both immediate and longer memory at all levels of cortical function.

A type of modification is required which:

(1) *Possesses the necessary properties of stability, accumulation, and recall.*

(2) *Eases the repetition of the complex activity patterns which produced it, so that a weaker or partial stimulus may be adequate.* (Memory, facilitation, etc.) This is the normal conception of the properties of engrams.

But a closer consideration suggests that (2) should be replaced by a stronger requirement (2*) which includes (2) as a special case:—

(2*) *Eases the repetition, generally in a simpler or more unified form, of the complex activity which produced it.* The facts regarding perception, memory and image formation, recognition, and perceptual and intellectual generalization, suggest that a process which tends to simplify activity patterns by preserving only their dominant features underlies the production of brain modifications. Generalization may be defined as the establishment of a single response corresponding to dominant features of a series of similar but not identical stimuli, and this leads directly to the requirement (2*).

Every record and image of past activity tends in general to simplify the phenomenon to which it corresponds and to involve a "loss of information." Brain modifications are probably in general structurally simpler than the activity patterns which produce them, and record only their quantitatively dominant components.

(3) *Is anisotropic, yielding privileged paths or channels in particular*

directions with sense. The privileged directions may not correspond to particular neurones; vector anisotropy is the essential feature.

(4) *Permits the combination of a high degree of neuronic localization of afferent and efferent patterns, e.g. in the sensory and motor areas, with extensive spread or multiple representation of activity patterns associated with the higher functions.*

There is evidence that the higher functions connected with the transformation of afferent into efferent patterns involve some degree of mass action, i.e. the synchronous activity of an extended region containing large numbers of neurones, possibly in addition to processes dependent on specific neuronic paths. The fact that complex activity patterns which are frequently repeated in slightly varying forms acquire a characteristic stability *as units* suggests that they do not depend on neuronic processes in particular cells. The functional organization of the cortex in relation to the higher functions appears to be in some degree independent of its fine cytological organization, only the larger structures being functionally significant. A satisfactory hypothesis must therefore be expected to throw light on the relation of micro-molecular-structural and neuronic activity to macro-field-functional and synchronous processes. For example a hypothesis would be helpful if it showed that "the separation into many parts and the union into a single whole are simply the two extremes on the scale of 'degree of connectedness' " (Ashby, 1952).

Any hypothesis should in the first instance meet the above requirements. Other problems, such as intensity of memory formation, conditions of recall, age effects, and learning by inhibition of non-adaptive activities, may be regarded as secondary.

The most interesting hypotheses which have been proposed fall into three classes:

A. *Structural changes in or between particular cells resulting from ordinary neurone activity*, such as fibre growth, development of new connexions between nerve-cell surfaces, structural changes producing permanent reduction of synaptic resistance, and molecular reorganization of contiguous cell surfaces. These mechanisms only cover strictly localized activity patterns, based on propagation along neurone surfaces; they give no hint of any mechanism of synchronization, integration, or simplification, and they neglect the functional equipotentiality of extended regions. Changes of these kinds probably occur, but alone they are inadequate.

B. *Chemical or metabolic changes in the neural cytoplasm.* Ordinary chemical changes are isotropic and cannot determine privileged directions. Thus the synthesis of new specific proteins is inadequate unless the new structures are regularly oriented.

C. *Self-maintaining or similar processes*, such as the persistence and summation of excitation, changes in synaptic efficiency under repeated

excitation, and reverberating circuits. These are unsuitable for long memory unless combined with a stable structural change. Even for short memory hypotheses of this type require to be strengthened by a precise biophysical description of the manner in which activity lowers synaptic thresholds.

The hypotheses of Class A are the most promising for stable memory but they appear to be unduly restricted in one respect: they assume the extension of a stable structure *whose position and orientation are fixed by the surfaces of a particular cell or set of cells.* But the facts appear to require a structural modification *whose position and orientation are fixed, not by the geometry of particular cells, but by the direction of propagation of synchronous pulses extending over many cells*, a direction determined by the larger structural features of the cortex. Thus the structural modifications underlying memory may be orientated in relation to the gross and medium scale anatomy of the cortex, and not to its basic cyto-architecture.

We can use general biological principles to discover how such functionally orientated modifications might be produced.

Most biological structures, in the course of their function, undergo cycles of electrical, chemical, and structural changes. They suffer rhythmic pulsations which display electrical, chemical, and structural aspects. We may therefore expect to find that the structural basis of memory lies in *pulsating* modifications of cortical material.

Again, most biological structures tend to develop in the course of their function. We should therefore look for a *self-developing pulsating structure*, i.e. one which is extended or strengthened in the course of the potential cycles which it records and facilitates.

Every differentiated structure and function of a multicellular organism may be regarded as the development of a less differentiated structure and function present in the original parent cell. The surface conduction along the neurones of the central nervous system corresponds to the propagation of pulses of polarization and depolarization on the surface of the parent cell. This suggests that the mass activities of the cortex may correspond to the propagation of spatially extended pulses of polarization and depolarization through the volume of the cytoplasm of the parent cell. While the rest of the nervous system is functionally organized in terms of neurone surfaces, part of the cortex may in relation to the higher functions be organized as an extended mass of neural cytoplasm, whose functional continuity is not interrupted by its subdivision into cells. The functional element underlying memory effects may be an effectively continuous region of neuroplasm in certain cells in particular cortical layers.

The question then arises: on this assumption *what kind of pulsating structural modification of the cortical cytoplasm, largely independent of its division into cellular units, can be produced by its pulsations so that the modification facilitates their repetition?*

Little is known regarding the condition of the cytoplasm in cortical

cells, either before or after functional activity has begun. But in certain layers and types of cell the cytoplasmic protein may at first be isotropic and display relatively little medium or long-range ordering, the polypeptide chains and fine cytoplasmic fibrils being oriented in all directions, as between one molecular region and the next (Monné, 1949). We shall assume that this isotropic cortical cytoplasm can convey pulses of depolarization and re-polarization through its bulk in any direction. In the rest of the central nervous system surface transmission predominates over volume transmission; in parts of the cortex the reverse may be true where functions involving memory are concerned.

The oscillations of electrical potential which constitute these pulses may be due either to the displacement of individual mobile charges or to changes in the total polarization of an extended structure considered as a unit. In either case the electrical cycles will be associated with structural cycles, the molecular structure of the protein or the arrangement of the fibrils undergoing cyclic changes. Thus in the course of the electrical cycles the protein structures will be worked to and fro along an axis coinciding with the direction of the changing action potential.

These structural and electrical pulsations are not necessarily best described as made up of localized processes affecting particular electrically charged groups, for they may also be represented as the co-operative action of an extended structure treated as a unit. The properties of electron mobility in proteins (hyper-conjugation of orbitals, semiconduction, etc.) as shown by Evans and Gergely (1949) and Eley *et al.* (1953) are such that a small electrical change at one point may affect the state of polarisation of an extended chain, or sheet, or volume of protein, the transformation being propagated at a high velocity. Thus in certain circumstances an extended region of cytoplasmic protein may be regarded as a co-ordinated system capable of unified nearly simultaneous activity, that is of undergoing unified cycles of electrical and structural changes as propagated pulses pass through the material in a given direction. If allowance is made for longer range electrical induction between the polarized cytoplasm of each cell and that of its neighbours, or for the possibility of some degree of structural continuity between neighbouring cells, such unified pulsations may well extend over an area, perpendicular to the direction of propagation, containing many thousands of cells.

What happens to the structural arrangement of the protein when such unified pulsations, composed of electrical and structural cycles, pass through it? What residual modification may remain after each cycle?

Certain types of disordered mechanical structures composed of rigid links possess the property, when worked to and fro in cycles, of tending to arrange themselves so that the working becomes easier. Such disordered systems may respond to cyclic forces by gradually ordering themselves so that progressively smaller amounts of energy are absorbed in each successive cycle. For example, if you work one piece to and fro in a pile of

metallic scrap, the movement becomes progressively easier. Similarly isotropic rubber subjected to cyclic deformations can acquire anisotropic properties so that it offers less resistance to the cycles. The cyclic force produces cumulative modifications in the previously chaotic system, which reduce the work per cycle.

We thus reach the following working hypothesis:

> *A polarization pulse passing through a region of cortical cytoplasm in a given direction may produce a cumulative residual effect by introducing an element of long-range anisotropic ordering into previously disordered protein chains or fibrils, or by increasing an existing element of such order, of such a kind that the region thereafter responds more easily to a repetition of the same stimulus.*

Similar but less definite suggestions have already been made by Whyte (1949, 1953) and Halstead (1951). Monné has stated that "memory must be associated with some permanent structural changes of the cytoplasm (cytoplasmic fibrils) of the neurones." But he considers mainly chemical changes (e.g. the synthesis of new specific proteins) as the basis of memory, whereas the present suggestion relies on the establishment of components of directional ordering in the already existing fibrillar texture of the neuroplasm.

The rhythmically pulsating cytoplasm may possess a self-moulding property, so that as it pulsates along a particular axis it tends to order its own structure, to work its parts into position in relation to the axes of polarization and propagation, with the result that the system repeats the pulsation more easily, with less energy consumption. In the course of pulsating, the molecular chains or fibrils are gradually worked into stable extended arrangements which can undergo single co-ordinated pulsations characterized by particular directions of polarization and propagation. As the same stimulus is repeated the corresponding overall ordering of the protein will be progressively strengthened until it becomes a stable differentiated channel for a pulse passing through a given region in a given direction and sense. Moreover such channels may possess a considerable cross-section perpendicular to the direction of propagation.

This cumulative medium- and long-range ordering of some of the protein chains throughout a particular volume of cortical cytoplasm is a kind of growth process of a pattern determined not by heredity but by activity, and involving the development not of a differentiated tissue but of an element of ordering in the molecular arrangement of an extended mass of cytoplasm. Here we are concerned with the *differentiation of particular vector directions*, possibly parallel to the cortical surface, in particular cortical layers. The templates of memory are not single localized molecular structures, but extended components of long-range order set at various angles to one another. Such long-range elements of pattern may

acquire a high stability enabling them to resist thermal, mechanical, and developmental disturbances.

This hypothesis appears in principle capable of satisfying conditions (1) and (4), but we must particularly consider (2*).

The ordering effect of the first occurrence of an activity pattern of a given form has to overcome a number of resistances, such as viscosity and the steric obstruction of the irregular chains, and only a small degree of ordering will result from one pulse. This means that the ordering will correspond only to the *statistically dominant pattern of activity*, or simplest overall pattern common to the successive activity patterns. Moreover this tendency to select the dominant pattern will be reinforced by the fact that the simplest overall patterns will be the most stable, since their parts will mutually support one another. The random protein structures may thus act as a structural sieve taking a stable impress at first only of the simplest, most unified, and statistically dominant component in all the patterns of activity of a given general form. While to any electrical cycle there may correspond an identical simultaneous structural cycle, the *stable* structural record is in general simpler than the electrical pulse which produced it.

On this view the cortical modification does not in general facilitate the identical repetition of the activity which produced it. This will only occur under special conditions when a stimulus which has been repeated identically a considerable number of times ceases to cause the accumulation of new subsidiary features and facilitates a fully stabilized pattern of activity, for example when learning, training, or detailed observation reaches completion. But this may be a limit which is never quite reached. In general the development of the modification proceeds from a grossly simplified to a less simplified and more accurate record. This process of the development of a hierarchically organized modification corresponds to Coghill's "progressive individuation" of behaviour patterns during ontogeny, and may hold the clue to the self-co-ordinating capacity of cortical processes.

This hypothesis, whether valid or not, may provide a fresh orientation and assist the design of new experiments. For it implies that in certain regions and layers, still to be identified, the functional element in relation to memory processes is not a cell assembly, a neural circuit or net, a synaptic pattern, or any other arrangement of cell surfaces, but an effectively continuous three-dimensional mass of cortical cytoplasm whose *cyto*-organization is irrelevant to its function and in which differentiated directions with sense determine its modes of operation. Even in ordinary neurones volume conduction and inter-neuronic induction effects must be present, though perhaps negligible; in parts of the cortex they may be dominant and surface effects negligible; while in other regions both modes may be simultaneously operative.

The hypothesis suggests that a single modification is represented by

one statistical component of long-range order, and that numbers of these may cross each small region of cortical cytoplasm without mutually interfering, as each is only invoked by a stimulus propagated in a particular direction. Thus around any small region the organization may be angular, possibly in a plane "parallel" to the cortical surface, and the cytoplasm in any one cell may possess many different modes of firing corresponding to different directions of propagation. The total organization of the higher functions may involve a vast set of superimposed statistical components of protein ordering each associated with a particular finite region and direction of propagation, which direction must be fixed with a definite accuracy since the incoming patterns come from and the outgoing patterns must ultimately reach localized channels. Thus a considerable extension of particular activity patterns, in a plane perpendicular to the direction of propagation, may be associated with rather sharp definition of that direction. The basic assumption, to be confirmed by direct or indirect experiments, is the presence in certain cortical regions of a *statistical spectrum of directional order around each point.*

On this view each complex memory-trace is a structurally stabilized, self-reinforcing, highly specific pulsation-mode. However, these traces do not operate in isolation, but as elements in a continuous transformation process leading in general from a complex sensory stimulus to a complex motor response. Here we have only considered one aspect of this transformation: the formation of facilitating modifications.

The excitation modes are organized in hierarchies extending from the simplest or dominant over-all pattern down to its most detailed components, corresponding to the hierarchies of motor patterns extending from gross features to fine components. The stupendous variety of memories corresponds to the very large number of ways in which the finest components may be combined into functional hierarchies.

The purpose of this note is to invite attention to the following questions which it is proposed to treat at a later date:

Experimental. Can physiological experiments be designed to test the hypothesis, directly or indirectly? It has been said that the cerebral cortex is the most difficult place in which to look for change with use. But the first thing is to have a clear idea of something to look for which can meet the known requirements.

Protein theory. Do existing views of the molecular structure of neuroplasmic or other protein show how repeated cycles of electrical depolarization and polarization might produce a cumulative long-range ordering of previously disordered components corresponding to the quantitatively dominant activity patterns, so that these dominant patterns are facilitated? If so, can biophysical experiments be designed to test the idea?

SUMMARY

It is suggested that in certain cortical regions cytoplasmic transmission supplements neurone surface transmission, and that the memory modification consists in the ordering through many cells of previously disordered or less ordered cytoplasmic protein chains or fibrils, in such a manner that the region thereafter responds more easily to repetition of the same stimulus. These extended orderings constitute pulsating structures which are reinforced by the activity which they facilitate. This hypothesis helps to account for properties which appear not to depend solely on the cyto-architecture of neuronic surfaces, such as synchronous mass action, pattern effects, and the fact that memory traces are normally simpler than the activity which they record.

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Notices of Recent Publications

On Aphasia. By Sigmund Freud. Authorised translation with an introduction by E. Stengel, M.D., M.R.C.P. 1953. Pp. 105. Imago Publishing Co. Ltd. Price 12s. 6d.

This book, first published in German in 1891 and now excellently translated by Dr. Stengel, is of more than merely historical interest. It shows how much neurology lost when Freud transferred his interest to psychiatry; it illustrates his debt to Hughlings Jackson and suggests that in developing his psychoanalytic concepts he drew upon Jackson's ideas; and, since the debate on aphasia is still fundamentally the same controversy as was raging sixty years ago, it may be read with profit as a contribution to current discussions.

Though Freud is remembered as the inventor of the term "agnosia," it is surprising that his views on aphasia have been so largely neglected, for his theory might have served as a bridge between the localizationists and their opponents.

Freud propounds his theory of the nature of aphasia as a critique of Wernicke's views. His approach is functional: just as a lesion of the arm area of the motor cortex usually causes, not a loss of certain isolated movements, but weakness of the arm as a whole, so a partial lesion of the motor speech area results in, not a loss of a particular hundred words, but "a general lowering of the functional activity of that centre." Similarly parts of the body are represented in the sensory cortex not as a topographical model, but in relation to function, as "a poem contains the alphabet." Indeed in his view the attempt to localize the psychological in terms of the physiological is an error in principle, whether it is applied to a whole mental faculty or to the simplest psychic element. The physiological correlate of an idea is a process, which is localizable only in the sense that its "pathways" are as important as its "centres."

Freud therefore rejects the view that "the speech apparatus consists of distinct centres separated by functionless areas, and that ideas (memories) serving speech are stored in certain parts of the cortex called centres while their association is provided exclusively by subcortical fibre tracts." For him the "centres" are merely cortical areas adjacent to "the cortical fields of the optic, auditory and motor cranial nerves," and they are important "only for the pathology, and not for the physiology of the speech apparatus." Hence a lesion near one of the centres produces a specific effect by cutting off one of the elements of speech association from its connexions with the others. A lesion situated centrally in the speech region, however, produces a more general functional disturbance, which Freud terms asymbolic aphasia, and which he regards as a disorder of the association between word concept and object concept. Freud then proceeds to apply the Jacksonian concept of "functional retrogression" to the interpretation of aphasic phenomena.

It has been said that every thinker is by nature either a Platonist or an Aristotelian. Similarly most neurologists seem to be attracted either to the localisationalist or the holistic interpretation of aphasia. Freud was holistic, and it would seem that many of the present generation of neurologists are in agreement with his conclusion "that the significance of the factor of localization for aphasia has been overrated, and that we should be well advised once again to concern ourselves with the functional states of the apparatus of speech."

W. R. B.

Pictorial Introduction to Neurological Surgery. By G. F. ROWBOTHAM and D. P. HAMMERSLEY. 1953. Pp. 108. E. and S. Livingstone, Ltd. Price 21s.

Mr. Rowbotham points out in his preface that the surgeon in a centre for the treatment of injuries may require several specialist skills. With this in mind he has, with the assistance of an artist, produced this small volume in which the technique of operations upon the scalp, skull and brain are described and illustrated. The surgical treatment of head injuries is dealt with in the latter half of the book. The descriptions of technique are lucid and the drawings of high quality so that the author's goal should be achieved.

J. E. A. O'C.

The National Hospital, Queen Square, 1860–1948. By SIR GORDON HOLMES. 1954. Pp. 98, plates 8. E. and S. Livingstone Ltd., Edinburgh. Price 10s. 6d.

For those who work in such institutions, it is not the largest and most imposing hospitals or medical schools that necessarily command the deepest allegiance or have the greatest hold upon their affections. Amongst hospitals, few indeed can have impressed more deeply the lives of its students, resident medical officers or consultant staff than the National Hospital, Queen Square.

Yet from what humble beginnings it arose, on what pathetically small resources it grew and lived, and under what recurrent financial stringency it continued to labour through the eighty-eight years of Sir Gordon Holmes' story.

Clearly, the writing of this history has been a work of filial piety, and is but one indication of many that could be adduced of the loyalty and affection the hospital has always inspired in those who have worked within its walls : whether over long periods as members of its permanent staff, or, more briefly, as students or residents who have left it to practise neurology elsewhere, or to return to the pursuit of the basic sciences that are its foundations, carrying with them the knowledge and stimulus they have gained there, over the whole English-speaking world, and beyond. For whoever may have enjoyed this experience, it is perhaps not easy to consider dispassionately the role which Queen Square has played as the cradle of British neurology, for it has coloured his entire outlook upon neurology and given him the sense that, in however inconspicuous a corner or subdued a tint, he has been woven into the rich fabric of its tradition.

Sir Gordon Holmes is the link between the past when the out-patient clinic, the ward, the pathological laboratory and post-mortem room were the sole and the essential workshops in which modern clinical neurology was fashioned, and the present era of rapid change in which the methods of many scientific disciplines have been called in to increase our diagnostic and therapeutic resources, and have so expanded the subject that in the eyes of the unwise they have overshadowed the clinical discipline. Thus, he is peculiarly fitted to record the almost ninety years of the hospital's life until its absorption in 1948 into the National Health Service, since for almost half of that period he has been part of this life.

His story opens with a brief chapter on the development of neurology from the time of Hippocrates to our own day, so that the reader may the more easily appreciate what was the state of the subject when the hospital first opened its doors in 1860. Only against this background can the achievement of the hospital be measured, and the quality and degree of its contribution to modern neurology be fully appreciated.

The succeeding chapters deal chronologically with its growth, its domestic and administrative milestones and ever-present difficulties, and the lives and passing

of the generations of its honorary staff, not entering upon the chronicle of those still living.

For those who have passed through the house as residents, all the chapters will have their interest, but for those who have not, and they must be the majority of its students, it is likely that the more personal chapters with their brief sketches of the figures of the long and the recent past will appeal more strongly, and what a procession of names they provide : of those who have enriched neurology by their ideas or by factual contributions of diverse kinds, and of those who have excelled as teachers and have thus formed the tradition of the hospital as the seat of an active school of the most precise of medical disciplines : that of clinical neurology and neuro-pathology.

Inevitably the generations of resident medical officers, from whose ranks for the most part the honorary staff was recruited, do not figure so prominently in these pages, yet they have been a vital element in the hospital's life, and doubtless the more recent of them could each contribute his own reminiscences of the strenuous and invigorating years he spent within its walls, of the personalities he strove to serve, and of their foibles, which he bore with and did his best to humour. Thus the book will have a great power of recall for very many who will read it.

In a Foreword, the Chairman of the hospital's Board of Governors, Sir Ernest Gowers, has paid a just tribute to the author, and his brief sketch of Sir Gordon Holmes will bring back memorable days to many of us. Yet historical justice also requires some expression of appreciation for what the Chairman has himself done for the renaissance of the hospital after the vicissitudes of the late war, and for his prudent and unselfish guidance of it through from the epoch of which this book tells to its present position under the State. This, too, has been a work of filial piety in the son of one of Queen Square's great figures, Sir William Gowers.

The book is beautifully produced by the publishers and has eight plates of the hospital and some past members of its staff.

F. M. R. W.

Preliminary Notice. The Fourth Symposium Neuroradiologicum will be held in London under the Presidency of Dr. James Bull, from September 13—September 17, 1955. Radiologists, Neurosurgeons, Neurologists and others interested will be most welcome. All wishing to contribute papers are invited to communicate as soon as possible with the Honorary Secretary, Dr. R. D. Hoare, at the National Hospital, Queen Square, London, W.C.1.